CELMODS ALONE AND IN COMBINATION IN NEWLY DIAGNOSED AND RELAPSED/REFRACTORY PATIENTS

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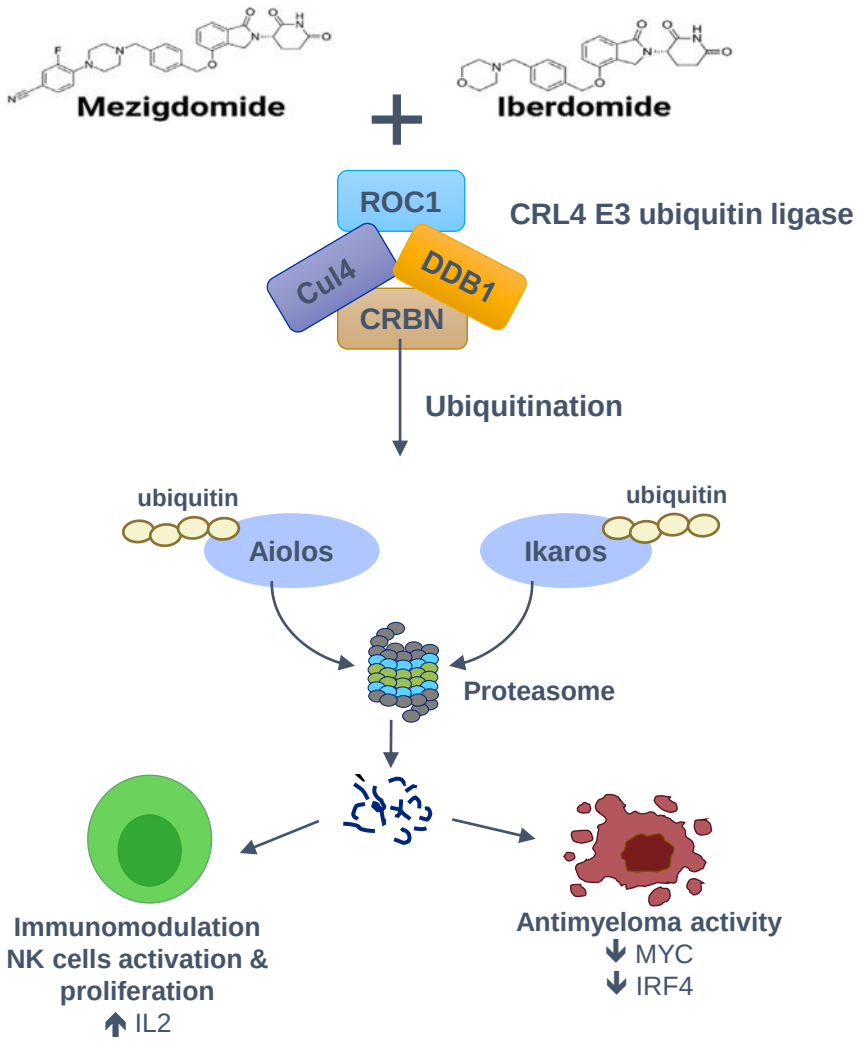
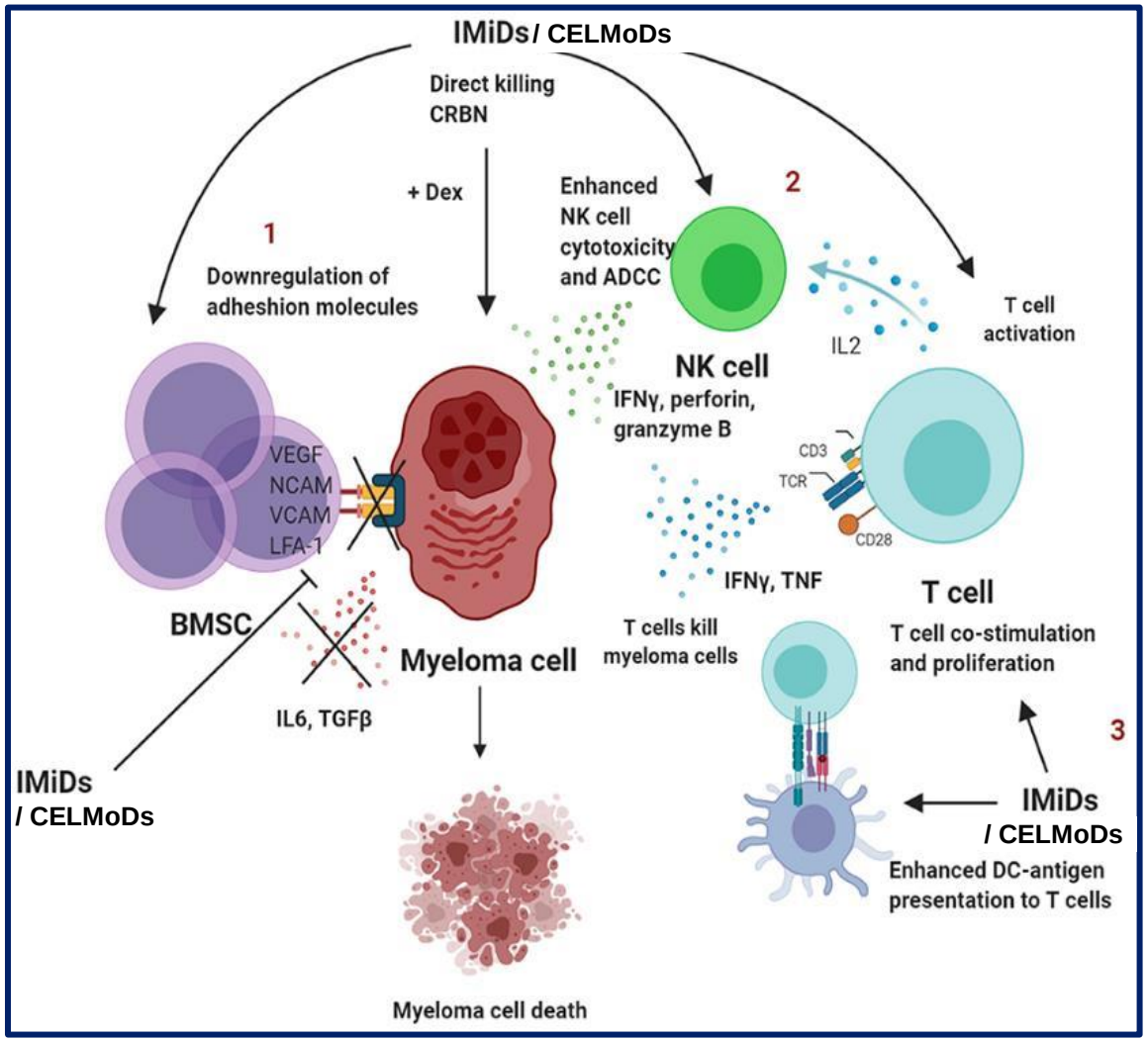
CELMODS: MECHANISM OF ACTION

CELMoDs bring the CRL4 E3 ligase and target proteins Ikaros and Aiolos into proximity to start protein degradation by the ubiquitin-proteasome system





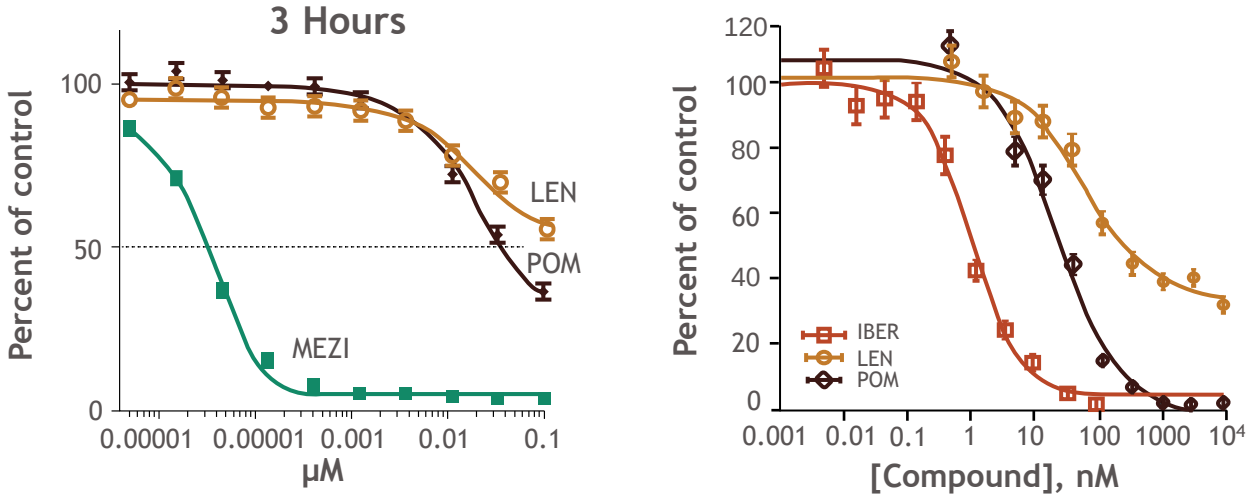
CELMoDs, cereblon E3 ligase modulators; IMiDs, immunomodulatory drugs

Patel, et al. *Clin Lymphoma Myeloma Leuk*. 2024 Nov;24(11):762-769.

IN PRECLINICAL MM MODELS, THE DISTINCT BIOCHEMICAL FEATURES OF NOVEL CELMOD AGENTS HAVE SHOWN ENHANCED ACTIVITY OVER CLASSIC IMIDS

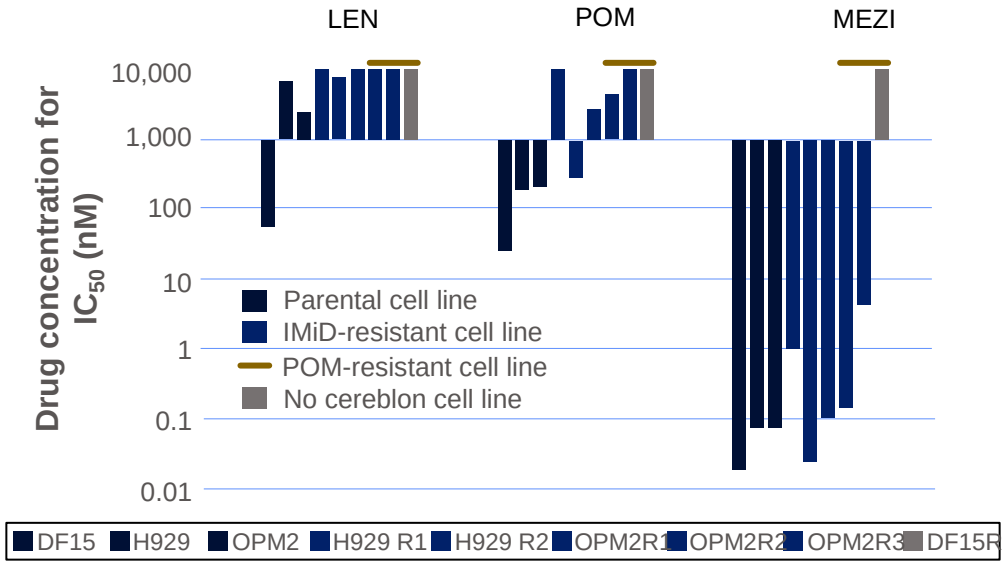
Protein degradation kinetics[1-3]

In vitro, IBER and MEZI are faster at Aiolos degradation, which can be achieved at lower concentrations compared to LEN and POM



Anti-proliferative activity[4]

Novel CELMoD™ agent induces superior anti-proliferative activity, including in IMiD-resistant cell lines

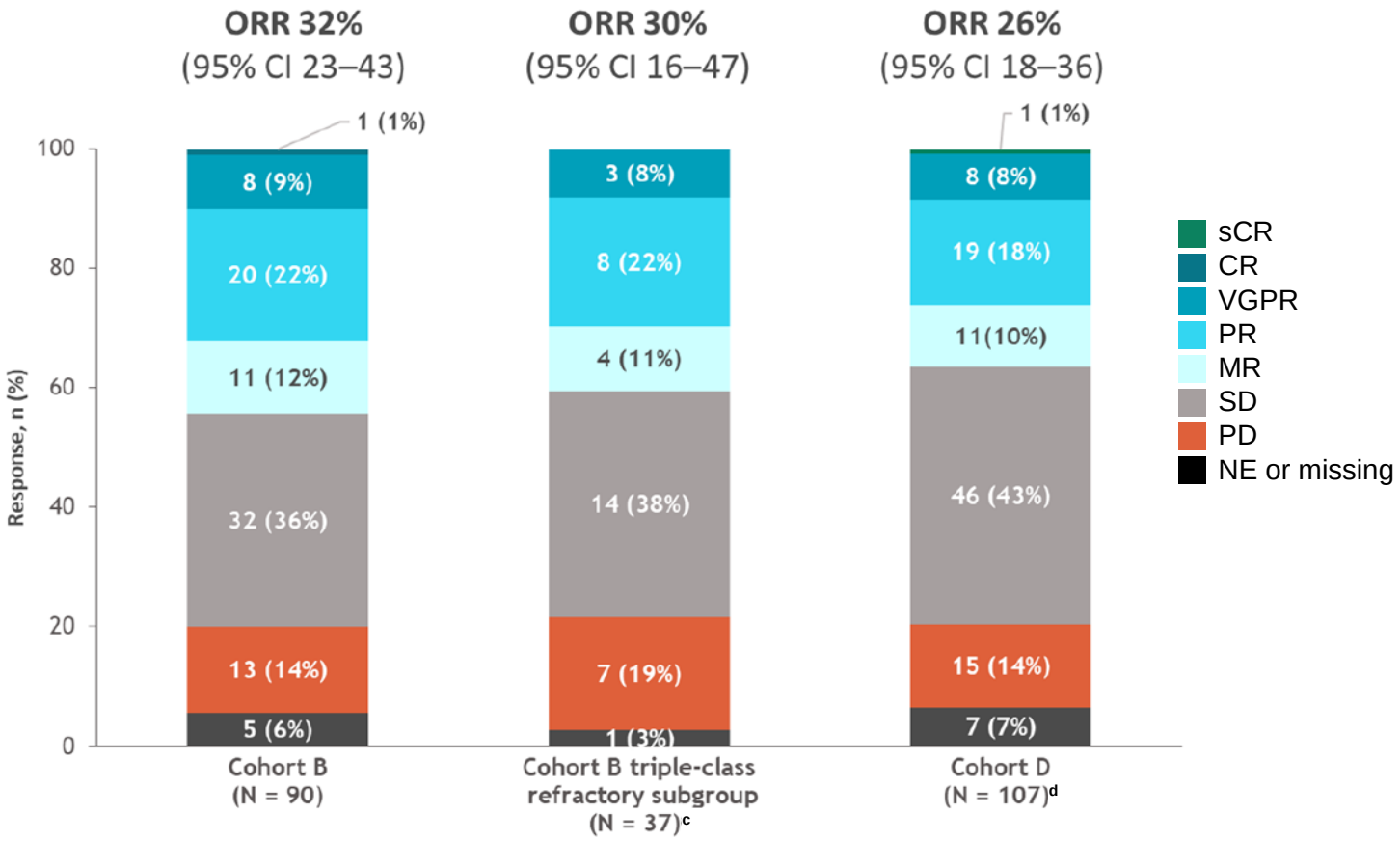


CELMoD, cereblon E3 ligase modulatory drug; IBER, iberdomide; IC_{50}, half maximal inhibitory concentration; IMiD, immunomodulatory drugs; LEN, lenalidomide; MEZI, mezigdomide; MM, multiple myeloma; POM, pomalidomide.

References: **1.** Hansen JD, et al. *J Med Chem.* 2020;63(13):6648-6676. **2.** Matyskiela M, et al. *J Med Chem*. 2018;61(2):535-542. **3.** Lopez-Girona A, et al. *Blood*. 2019;134(suppl 1):1812. **4.** Richardson PG, et al. Presented at 2020 ASCO Annual Meeting [abstract 8500].

IBER+DEX DEMONSTRATED CLINICAL ACTIVITY, EVEN IN HEAVILY PRETREATED PATIENTS REFRACTORY TO CLASSIC IMID AGENTS

Baseline characteristics[1]	Dose esc[a] (n = 90)	Dose exp[b] (n = 107)
Median prior lines	5 (4-8)	6 (5-8)
IMiD-refractory LEN-refractory POM-refractory	96% 84% U%	100% 85% 95%
PI-refractory	78%	97%
CD38-mAb refractory	74%	100%



[a]Dose escalation cohort received doses of oral IBER from 0.3-1.6 mg on 21/28-day schedule plus oral DEX (40 mg [20 mg if age >75 years] once per week). [b]Dose expansion cohort received the recommended phase 2 dose (1.6 mg) of oral Iberdomide plus oral DEX (40 mg [20 mg if age >75 years] once per week). [c]Dose-escalation cohort triple-class refractory subgroup had received at least three previous lines of therapy and had triple-class refractory disease. [d]Two patients who had stable disease and minimal response discontinued treatment because of death due to COVID-19.

References: 1. Lonial S et al. *Lancet Haematol*. 2022;S2352-3026(22)00290-3. **2.** van de Donk NWCJ, et al. Presented at 2022 IMS Annual Meeting [abstract P-279].

SAFETY PROFILE SUMMARY FOR IBER REGIMENS

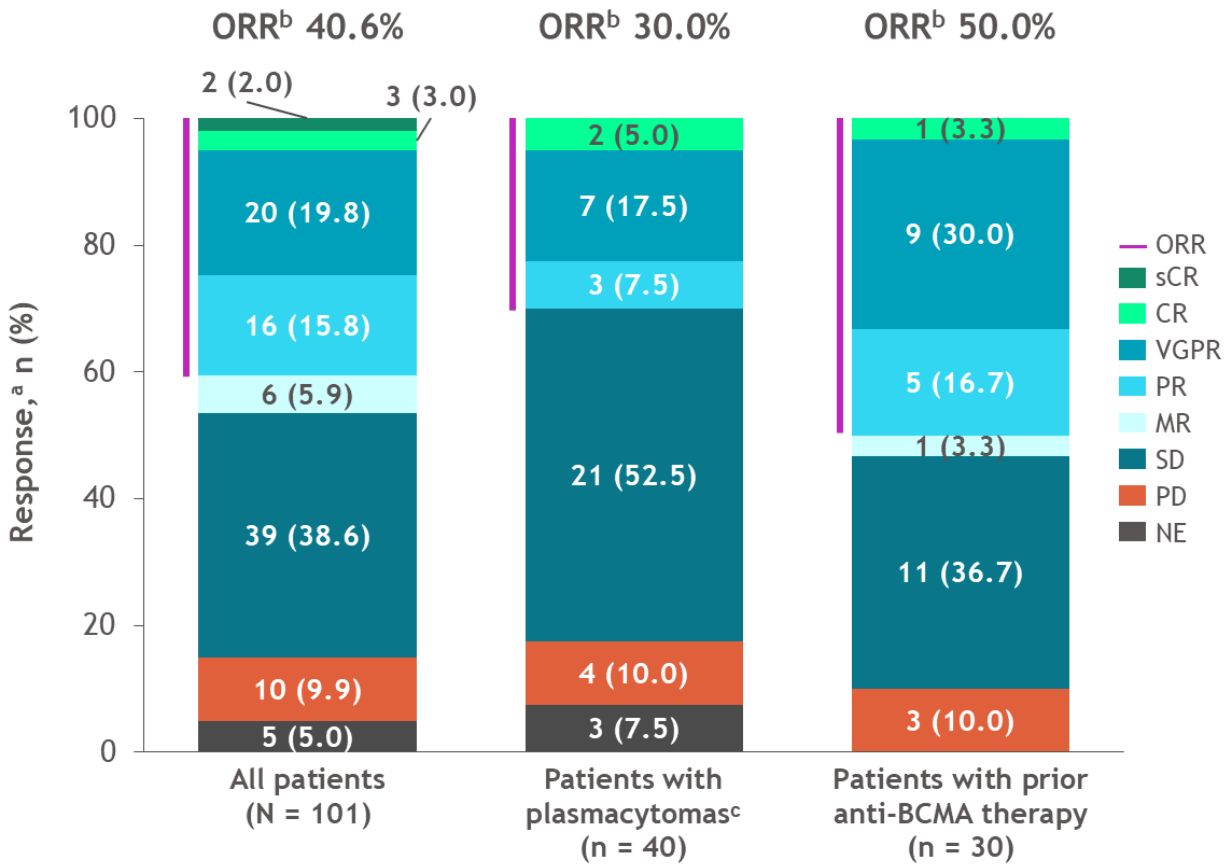
TEAEs of interest, n (%)	IBER-d[1] (n = 107) MM-001 Cohort D			IBER-Dd[2] (n = 39) MM-001 Cohort E			IBER-Vd[2] (n = 25) MM-001 Cohort F			IBER-Kd[2] (n = 9) MM-001 Cohort G		
	All	Gr3	Gr4	All	Gr3	Gr4	All	Gr3	Gr4	All	Gr3	Gr4
Hematologic TEAEs												
Neutropenia	64 (59.8)	27 (25.2)	21 (19.6)	27 (69.2)	5 (12.8)	21 (53.8)	9 (36.0)	5 (20.0)	2 (8.0)	3 (33.3)	2 (22.2)	1 (11.1)
Febrile neutropenia[a]	5 (4.7)	4 (3.7)	1 (0.9)	2 (5.1)	1 (2.6)	1 (2.6)	0	0	0	0	0	0
Thrombocytopenia	38 (35.5)	7 (6.5)	16 (15.0)	13 (33.3)	3 (7.7)	2 (5.1)	9 (36.0)	1 (4.0)	5 (20.0)	2 (22.2)	0	1 (11.1)
Anemia	44 (41.1)	30 (28.0)	0	12 (30.8)	8 (20.5)	0	6 (24.0)	3 (12.0)	0	2 (22.2)	0	0
Non-hematologic TEAEs												
Fatigue	25 (23.4)	2 (1.9)	1 (0.9)	11 (28.2)	1 (2.6)	0	8 (32.0)	0	0	3 (33.3)	1 (11.1)	0
Diarrhea	25 (23.4)	1 (0.9)	0	7 (17.9)	1 (2.6)	0	6 (24.0)	1 (4.0)	0	3 (33.3)	0	0
Constipation	23 (21.5)	0	0	5 (12.8)	0	0	5 (20.0)	0	0	-	-	-
Rash	21 (19.6)	3 (2.8)	0	3 (7.7)	0	0	4 (16.0)	1 (4.0)	0	-	-	-
Peripheral neuropathy[b]	-	-	-	3 (7.7)	0	0	8 (32.0)	0	0	2 (22.2)	0	0
Thrombotic event[c]	-	-	-	0	0	0	0	0	0	0	0	0
Infections	62 (57.9)	26 (24.3)	3 (2.8)	23 (59.0)	4 (10.3)	2 (5.1)	17 (68.0)	4 (16.0)	1 (4.0)	7 (77.8)	2 (22.2)	1 (11.1)
Upper respiratory tract infection	11 (10.3)	1 (0.9)	0	11 (28.2)	0	0	9 (36.0)	2 (8.0)	0	2 (22.2)	0	0
Discontinuations due to AEs	**4.7%**			**2.3%**			**8.0%**			**11.1%**		

Clinical safety data highlight a **consistent tolerability profile** in all IBER regimens, with **low rates of non-hematological AEs** like fatigue, rash, and GI toxicities[1,2]

Low rates of discontinuations due to AEs were observed[1,2]

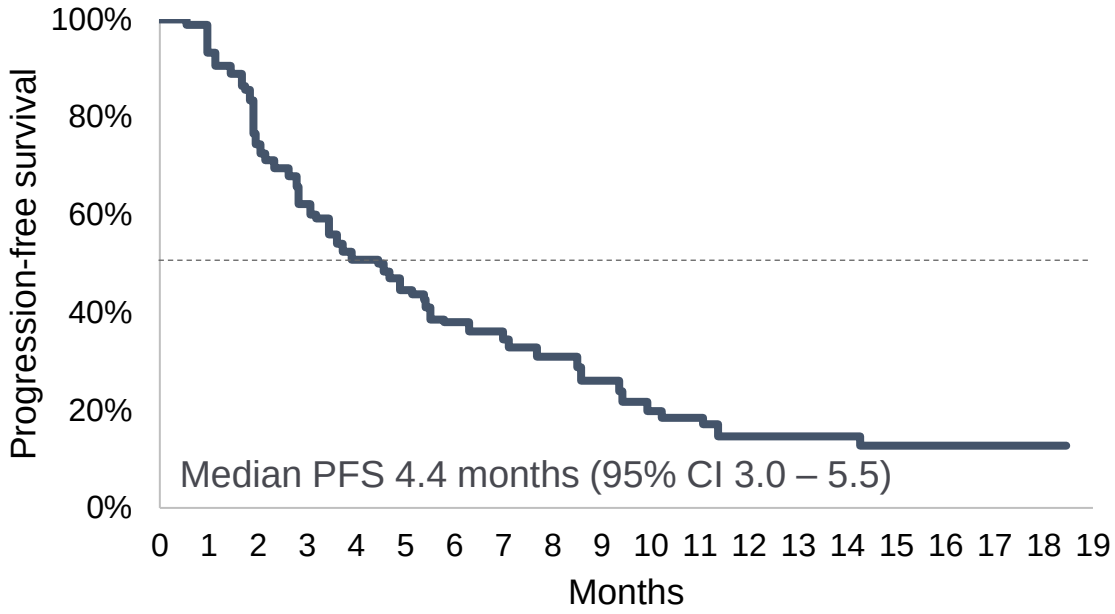
References: 1. Lonial S, et al. *Lancet Haematol*. 2022; S2352-3026(22)00290-3. **2.** Lonial S, et al. Presented at 2021 EHA Annual Meeting [abstract S187].

MEZI+DEX: RESPONSE RATES



Progression-Free Survival

Median follow-up 5.46 months



DOR, median (95% CI), months	
7.6 (5.4-9.5)	
Time to first response, median (range), months	
All patients	0.95 (0.89-12.92)

Activity of MEZI+DEX is promising in triple-class refractory patients, as well as those with plasmacytoma or prior anti-BCMA therapy

Reference: Richardson PG, et al. Presented at 2022 ASH Annual Meeting [abstract 568].

SAFETY PROFILE SUMMARY OF MEZI REGIMENS

TEAEs of interest, n (%)	MEZI-d[1,a] (N = 101) CC92480-MM-001			MEZI-Vd[2,b] (N = 28) CC92480-MM-002 Cohort A			MEZI-Vd (1.0 mg)[2,b] (N = 38) CC92480-MM-002 Cohort D			MEZI-Kd[2,b] (N = 26) CC92480-MM-002 Cohort C		
	All	Gr3	Gr4	All	Gr3	Gr4	All	Gr3	Gr4	All	Gr3	Gr4
Hematologic TEAEs												
Neutropenia	78 (77.2)	22 (21.8)	54 (53.5)	14 (50.0)	8 (28.6)	1 (3.6)	27 (71.1)	16 (42.1)	4 (10.5)	11 (42.3)	7 (26.9)	2 (7.7)
Thrombocytopenia	43 (42.6)	14 (13.9)	14 (13.9)	10 (35.7)	3 (10.7)	3 (10.7)	18 (47.4)	6 (15.8)	4 (10.5)	7 (26.9)	1 (3.8)	2 (7.7)
Anemia	53 (52.5)	35 (34.7)	1 (1.0)	11 (39.3)	4 (14.3)	0	15 (39.5)	3 (7.9)	0	5 (19.2)	2 (7.7)	0
Non-hematologic TEAEs												
Fatigue	36 (35.6)	5 (5.0)	0	-	-	-	12 (31.6)	2 (5.3)	0	7 (26.9)	1 (3.8)	0
Diarrhea	31 (30.7)	3 (3.0)	0	11 (39.3)	3 (10.7)	0	14 (36.8)	4 (10.5)	0	10 (38.5)	2 (7.7)	0
Constipation	24 (23.8)	0	0	7 (25.0)	0	0	13 (34.2)	0	0	-	-	-
Rash	-	-	-	-	-	-	-	-	-	-	-	-
Peripheral sensory neuropathy	-	-	-	9 (32.1)	0	0	15 (39.5)	0	0	-	-	-
Infections	66 (65.3)	29 (28.7)	6 (5.9)	15 (53.6)	1 (3.6)	1 (3.6)	25 (65.8)	8 (21.1)	2 (5.3)	11 (42.3)	4 (15.4)	1 (3.8)
Upper respiratory tract	-	-	-	6 (21.4)	0	0	-	-	-	-	-	-
COVID-19	17 (16.8)	7 (6.9)	0	1 (3.6)	0	0	9 (23.7)	3 (7.9)	0	5 (19.2)	4 (15.4)	1 (3.8)
Pneumonia[c]	22 (21.8)[d]	13 (12.9)[e]	3 (3.0)[f]	-	-	-	5 (13.2)	3 (7.9)	1 (2.6)	-	-	-
Discontinuations due to AEs	**5.9%**			**7.1%**			**13.2%**			**15.4%**		

Overall, MEZI regimens have a manageable safety profile[1,2]

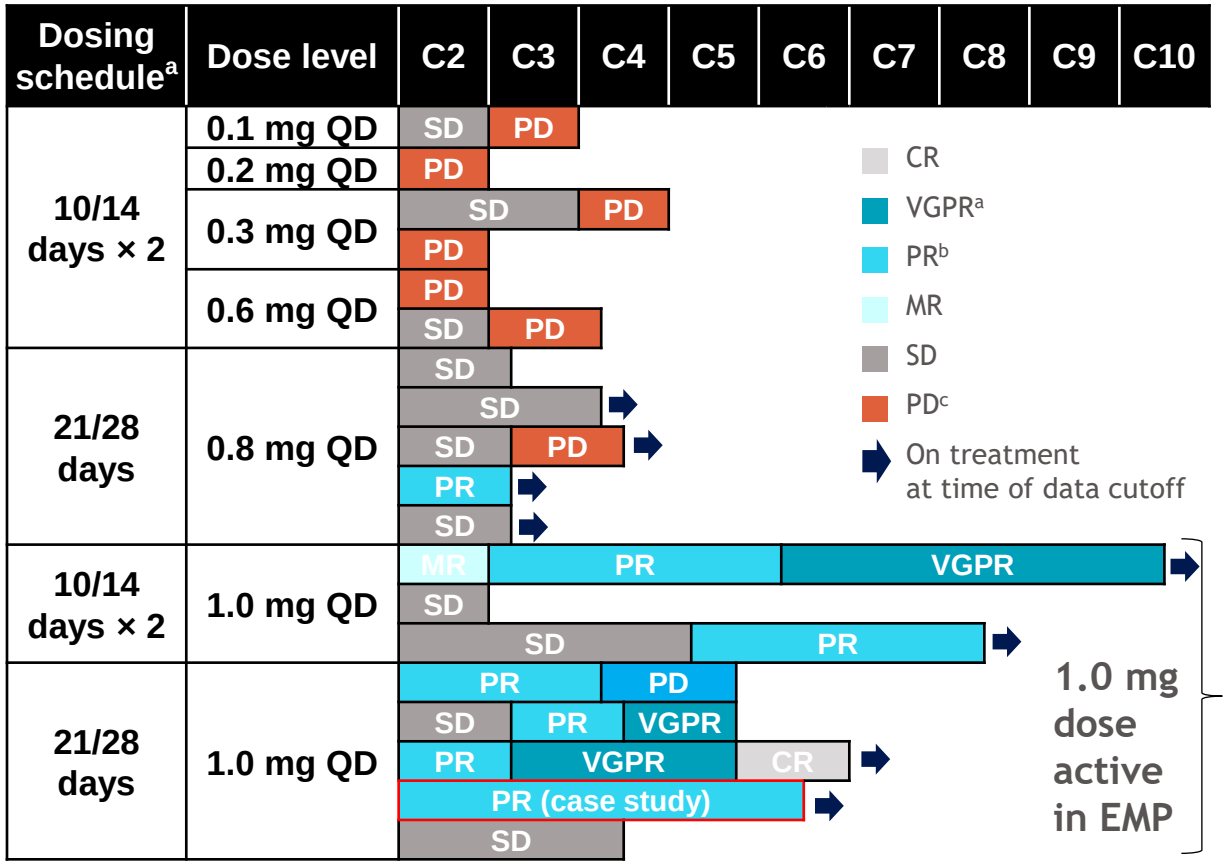
While **Gr3/4 neutropenia** is frequent, manageable with GCSF and dose modifications/ delays, and there are relatively **low rates of non-hematologic AEs**[1,2]

Note: Due to differences in patient population and trial design, conclusions from cross trial comparison are limited.

[a]Data cutoff: September 16, 2022. [b]Data cutoff: July 18, 2022. [c]Including all preferred terms for pneumonia [d]9 pneumonia NOS, 6 *Pneumocystis jirovecii* pneumonia, 2 COVID-19 pneumonia, 2 viral pneumonia, 1 bacterial pneumonia, 1 *Haemophilus* pneumonia, and 1 *Pseudomonas* pneumonia. [e]6 pneumonia NOS, 2 *Pneumocystis jirovecii* pneumonia, 2 COVID-19 pneumonia, 1 viral pneumonia, 1 *Haemophilus* pneumonia, and 1 *Pseudomonas* pneumonia. [f]1 pneumonia NOS, 2 *Pneumocystis jirovecii* pneumonia.

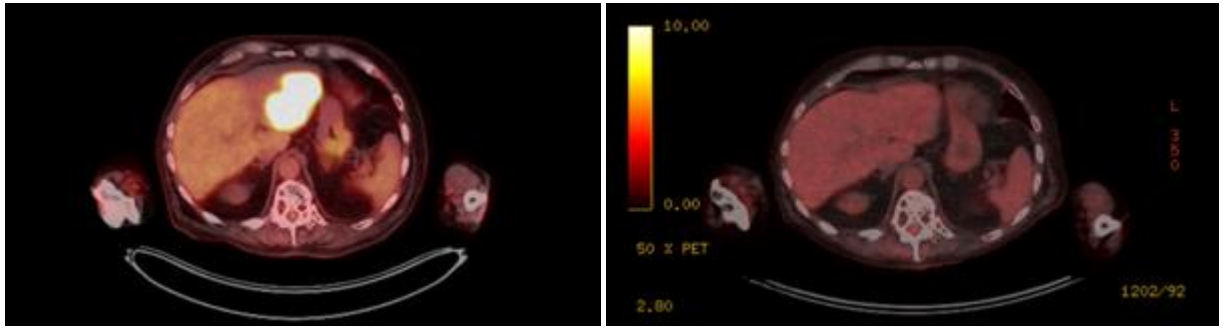
References: 1. Richardson PG, et al. Presented at 2022 ASH Annual Meeting [abstract 568]. **2.** Richardson PG, et al. Presented at 2022 IMS Annual Meeting [abstract OAB-053].

EARLY CLINICAL STUDIES SHOWED THAT MEZI+DEX TREATMENT INDUCES RESPONSES IN PATIENTS WITH PLASMACYTOMAS



PET scan pretreatment

PET scan post-MEZI C3D1



In a subset analysis of CC-92480-MM-001 phase 1/2 trial, MEZI+DEX treatment shows activity in patients with EMP[1]

[a]1 patient in the 21-/28-day 1.0 mg QD cohort had an unconfirmed VGPR as of the data cutoff date. [b]1 patient in the 21-/28-day 0.8 mg QD cohort had an unconfirmed PR as of the data cutoff date. [c]1 patient in the 21-/28-day 0.8 mg QD cohort had an unconfirmed PD as of the data cutoff date.

C, cycle; CR, complete response; D, day; DEX, dexamethasone; EMP, extramedullary plasmacytoma; MEZI, mezigdomide; MR, minimal response; PD, progressive disease; PET, positron emission tomography; PR, partial response; QD, once daily; SD, stable disease; VGPR, very good partial response.

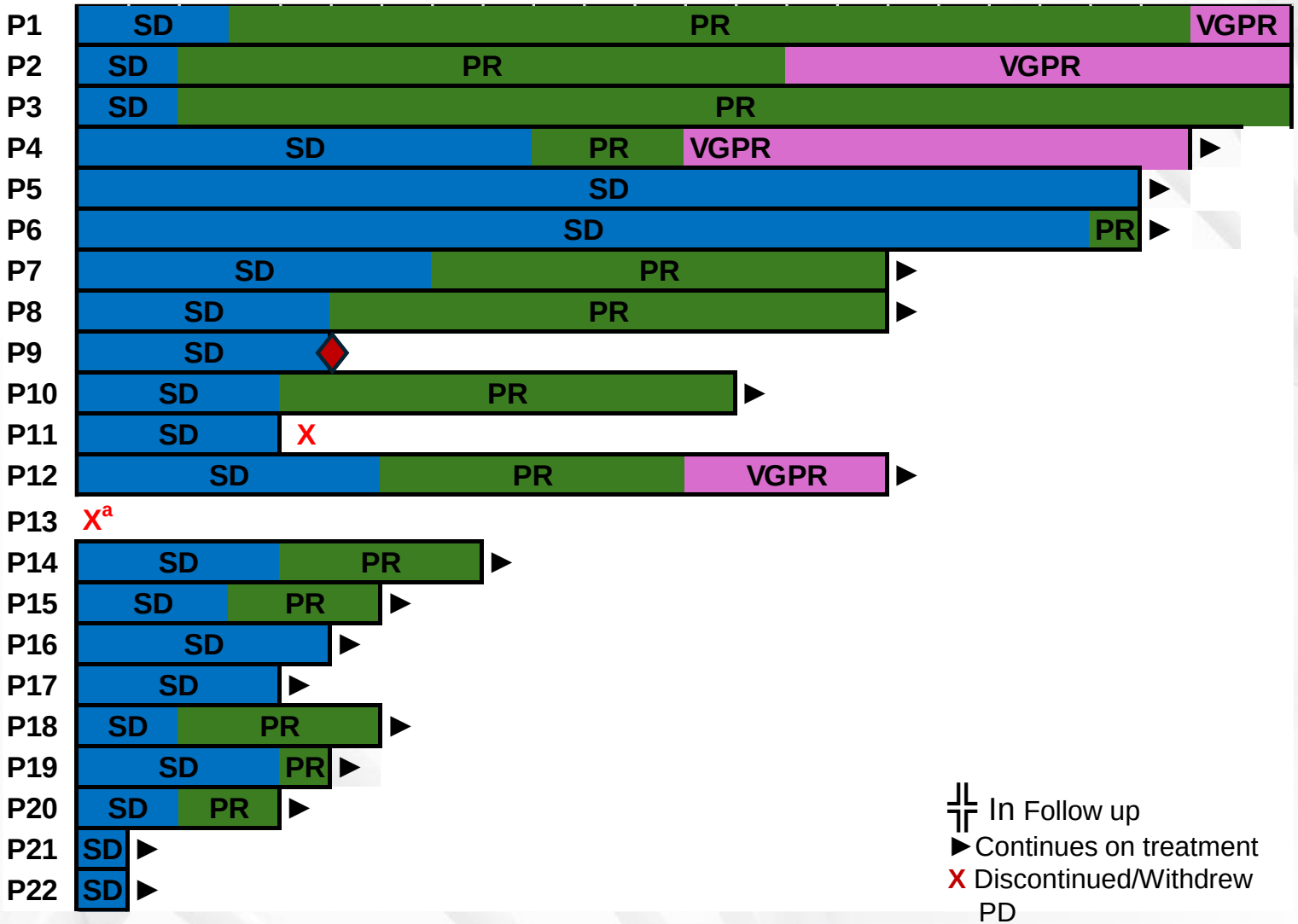
Reference: Richardson PG, et al. Presented at 2020 ASCO Annual Meeting [abstract 8500].

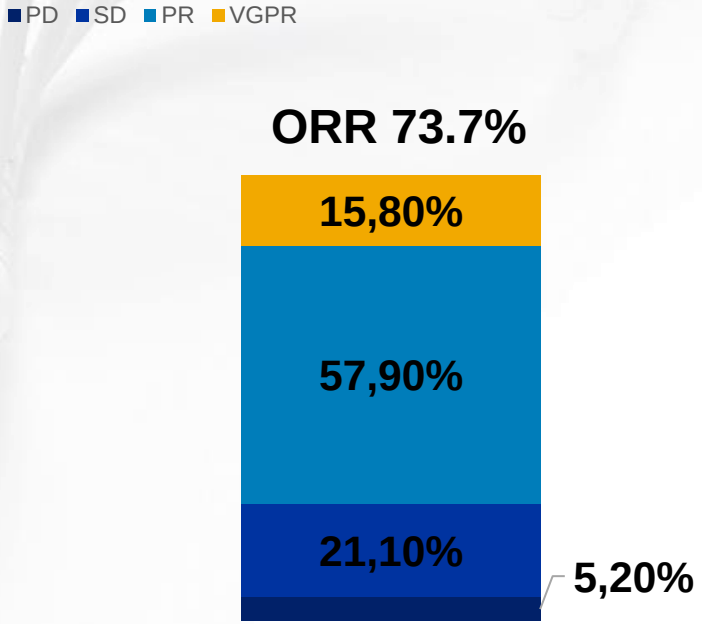
CLINICAL DEVELOPMENT OF THE CELMODS

Precursor	NDMM	Post-ASCT Maintenance	Early Relapse	Late Relapse
• Iber +/dex • Iber/Isa/dex	• Iber/Dara/dex	• EMN26 • EXCALIBER: Iber maintenance	• SUCCESSOR-1 • SUCCESSOR-2 • EXCALIBER-RRMM	• CC-220-001 • CC-92480-001 and 002 • CA057-003 • Iber + BsAb • Mezi + BsAb

Ongoing clinical trial development pre-and post-CAR-T cell therapy and with other emerging novel therapies

IBER IN INT/HIGH-RISK SMOLDERING MYELOMA





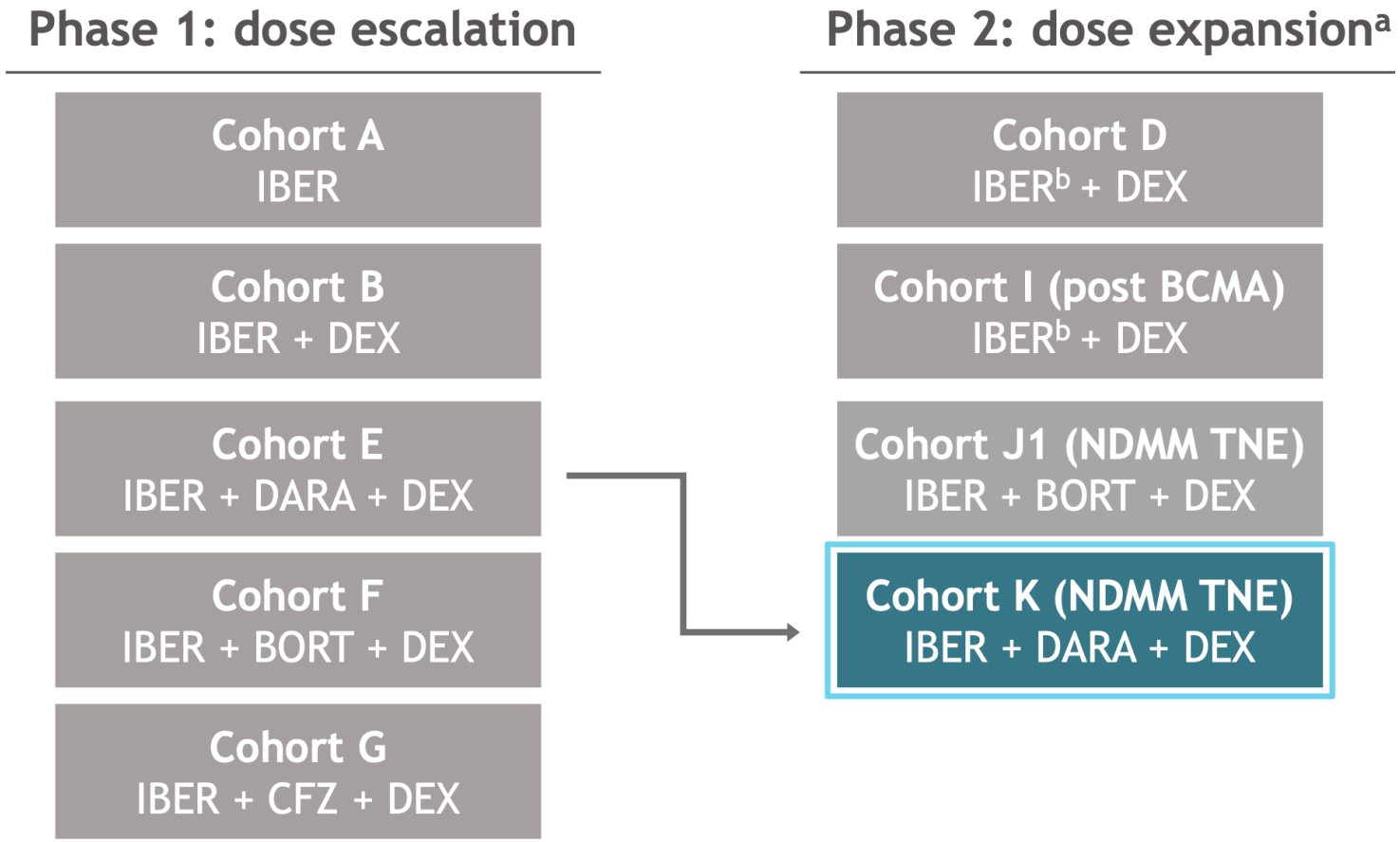
No Grade 3-4 non-hematologic AEs

No grade 3-4 hematologic AEs(neutropenia) at reduced 1.0 mg dose

Joseph et al; *Blood* (2024) 144 (Supplement 1): 1983.

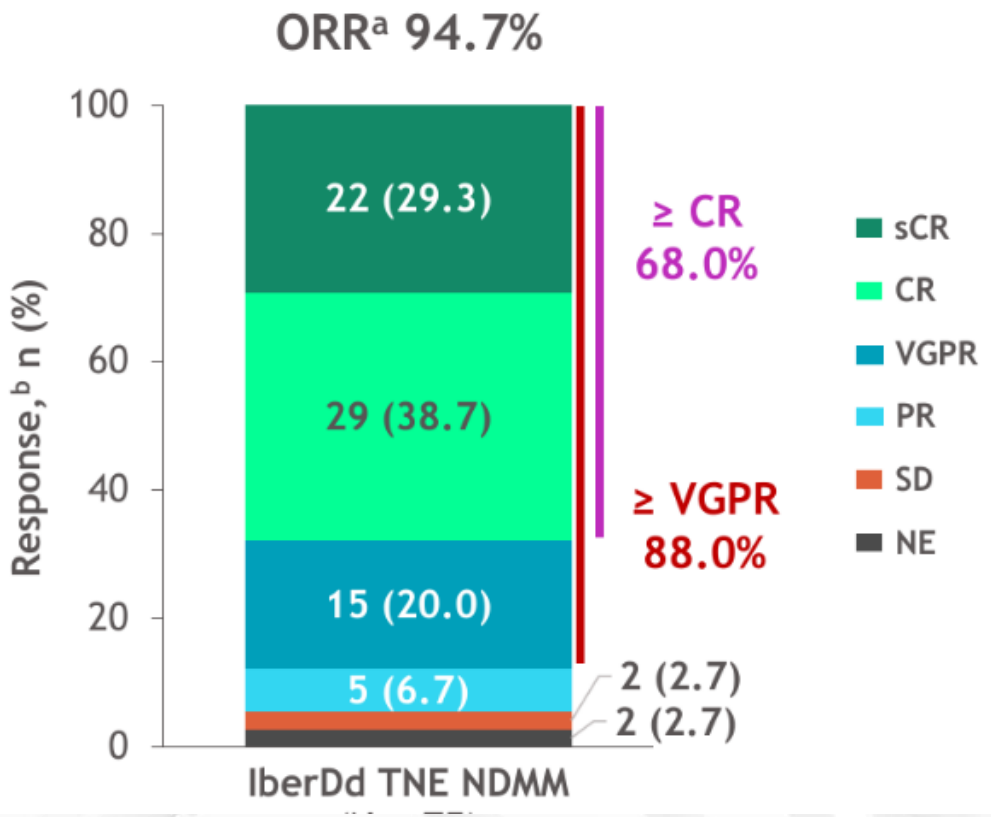
CC-220-MM-001 study design and objective

- Phase 1/2 trial evaluating IBER with different treatment combinations in MM[1,2]
- **Objective:** to report updated results with extended follow-up from the IberDd dose-expansion cohort of the CC-220-MM-001 trial in patients with NDMM who are TNE or not receiving ASCT as their first therapy



Sureda Balari A, et al. IMS 2025. Presentation OA-50

CC-220-MM-001: DARATUMUMAB + IBER



MRD negativity (10^{-5}) rates[c]

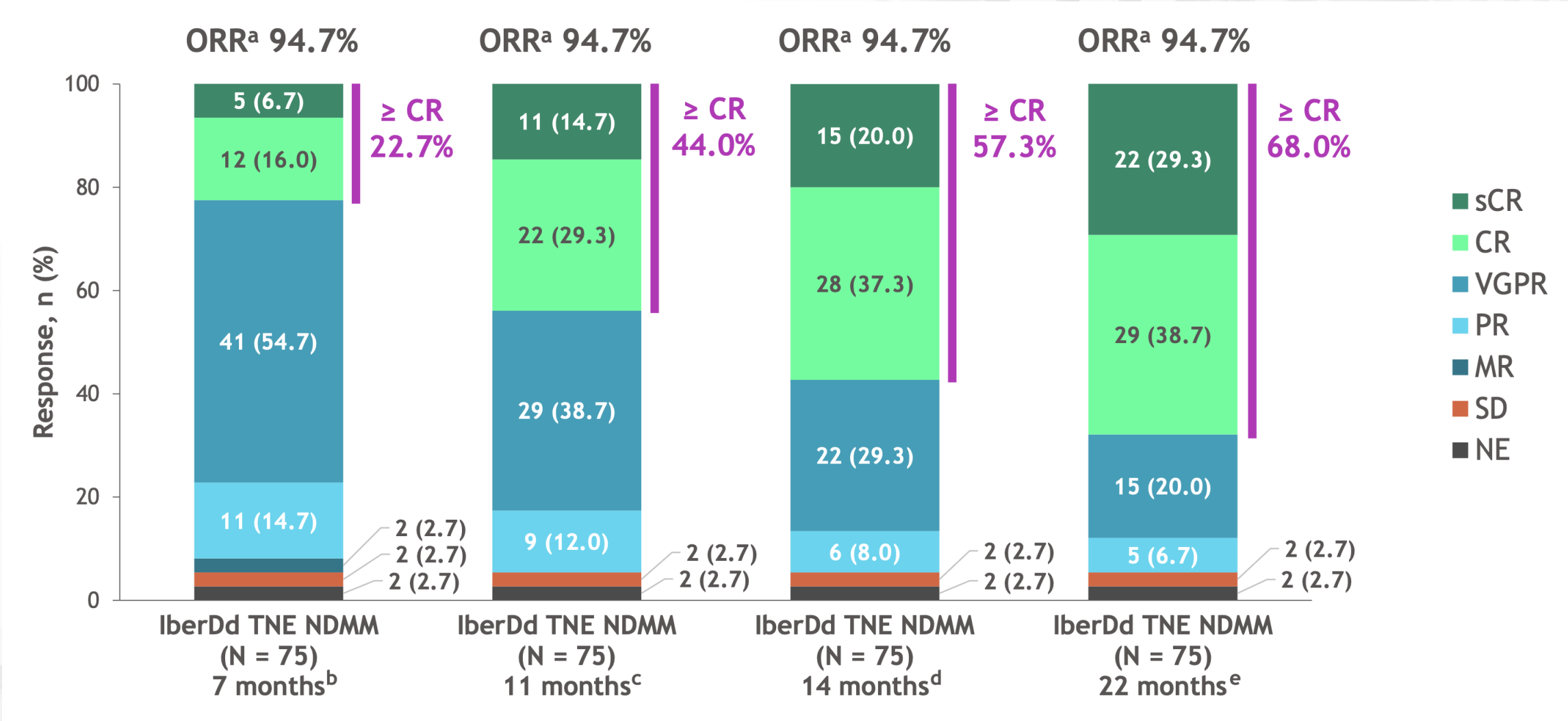
MRD negativity rate, n (%)	MRD negativity rate with ≥ CR, n (%)
48 (64.0)	42 (56.0)

Time to first response and duration of response

TTFR, median (range), months	DOR,[d] median (range), months
1.0 (0.9-11.3)	NR (NR-NR)

Sureda Balari A, et al. IMS 2025. Presentation OA-50

RESPONSES DEEPEN OVER TIME



Sureda Balari A, et al. IMS 2025. Presentation OA-50

EMN26: IBER MAINTENANCE POST-ASCT

Key eligibility criteria

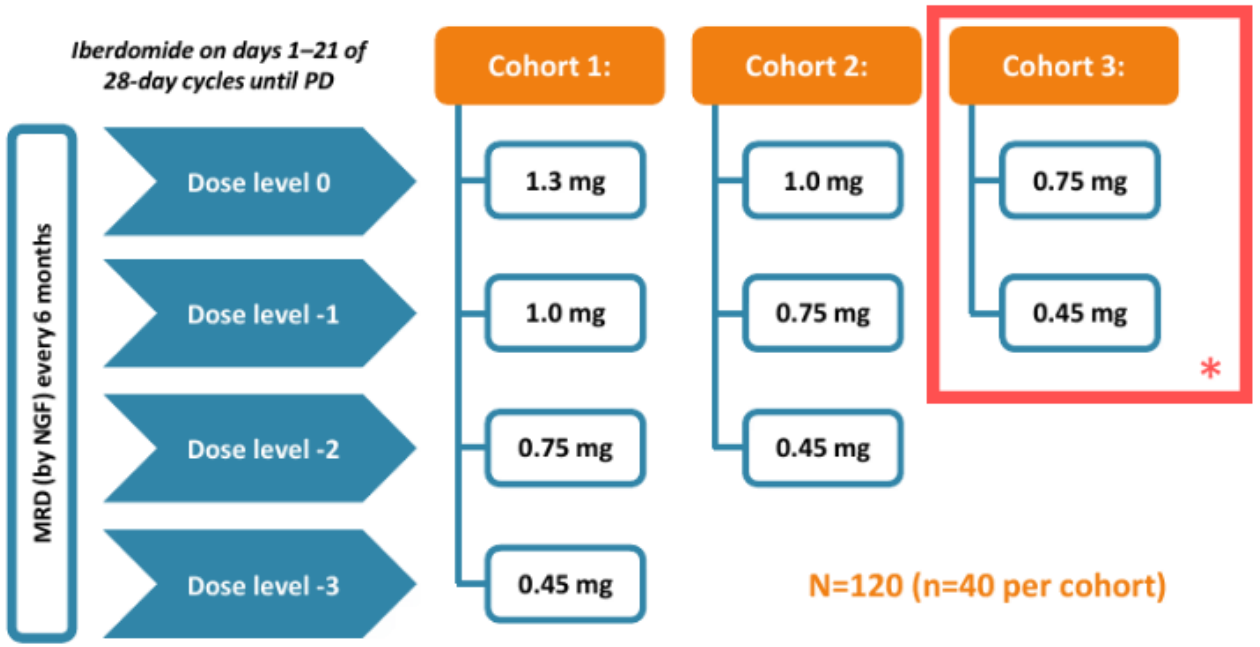
- NDMM patients, ≥PR after ASCT.
- Patients treated with proteasome inhibitor plus immunomodulatory drug-based induction (3-6 cycles), followed by single or double autologous stem-cell transplant (ASCT) with melphalan as conditioning regimen +/- consolidation.
- Patients within 15 months from diagnosis and 120 days after last ASCT or consolidation treatment, if performed.

Primary endpoint

- Efficacy (response improvement within 6 months: PR to ≥VGPR; VGPR to ≥CR; CR to sCR) of the 3 different dose levels of iberdomide maintenance post-ASCT.#

Key secondary endpoints

- Rate of next-generation flow (NGF) minimal residual disease (MRD; 10-5) conversion from positive to negative status
- Rate of adverse events
- PFS, PFS2, OS, TTP, TTNT

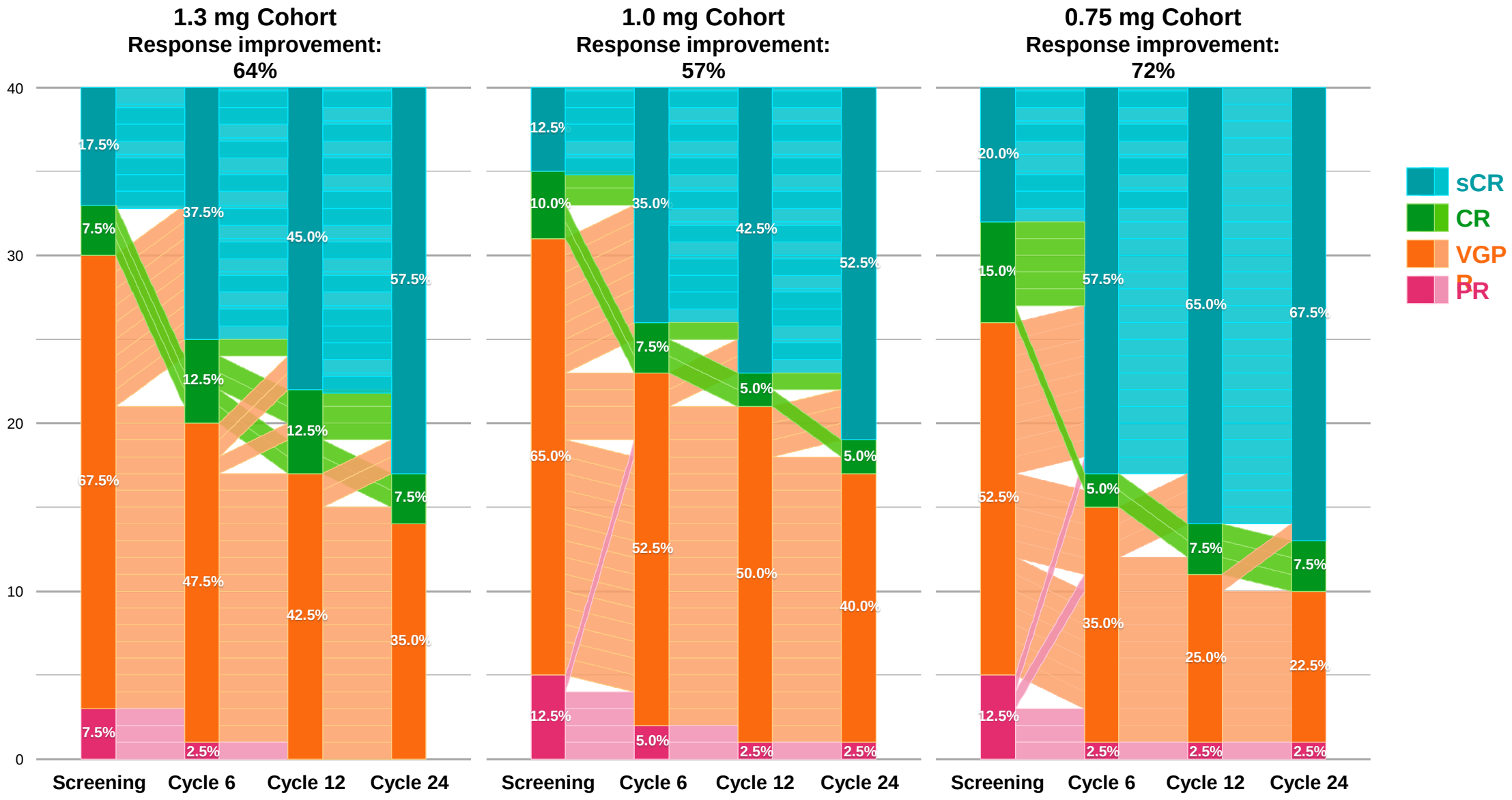


*Cohort 3 was added at a later stage.

Null hypothesis: response improvement rate within 6 month is ≤20%.

Van de Donk, ASH 2025, oral abstract #101

RESPONSE IMPROVEMENT ACROSS 24 CYCLES



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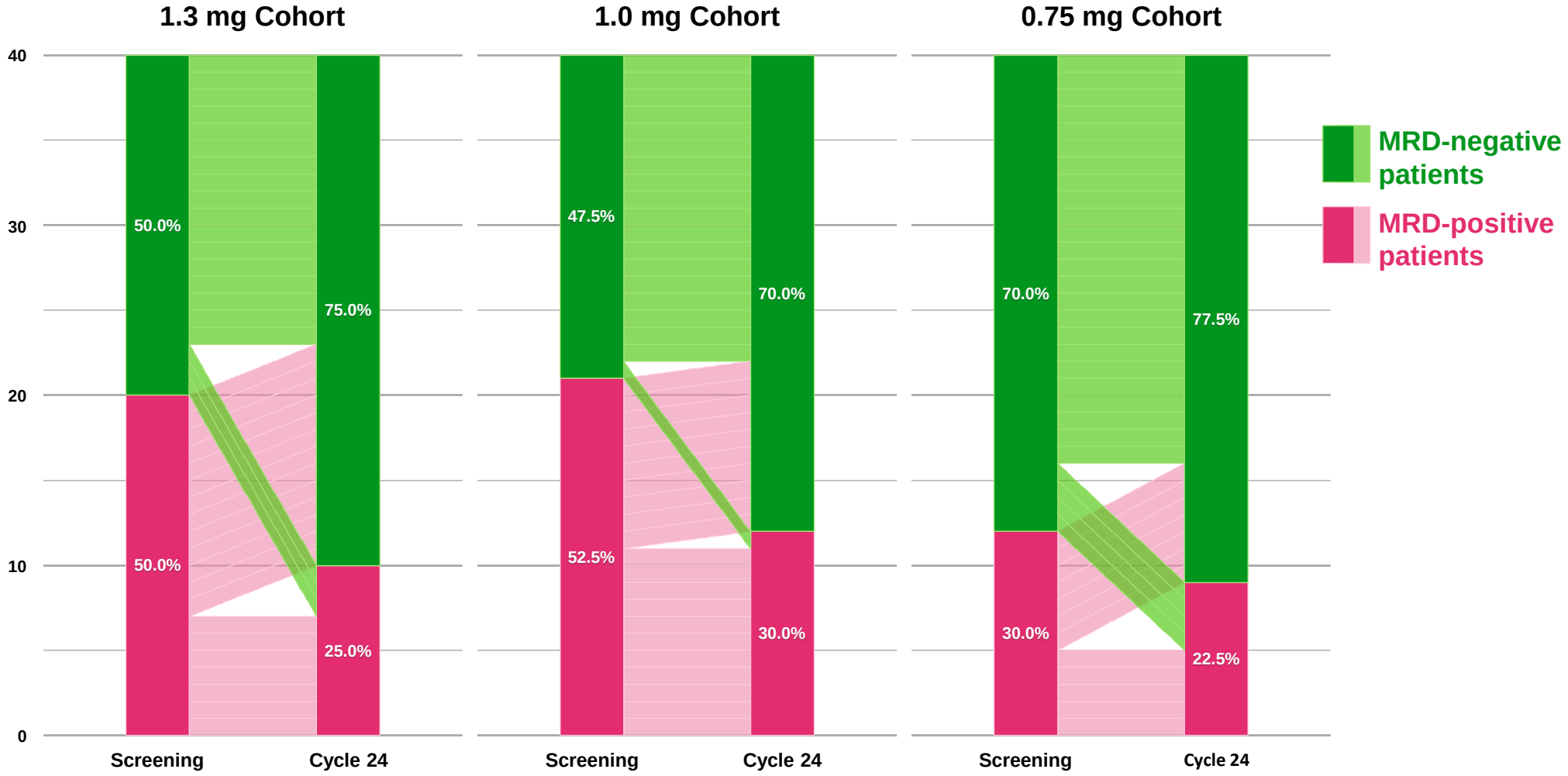
sCR, stringent complete response; CR, complete response, VGPR, very good partial response; PR, partial

MRD IMPROVEMENT DURING IBERDOMIDE MAINTENANCE



MRD was evaluated by next-generation flow cytometry (NGF) with a sensitivity of 10^{-5}.
Patients who experienced earlier study discontinuation in the absence of MRD evaluation were included in the denominator.

Van de Donk, ASH 2025, oral abstract #101

MRD, minimal residual disease; NGF, next-generation flow cytometry.

STUDY DESIGN: EXCALIBER MAINTENANCE (IBER VS LEN IN NDMM)

Objective: To compare the efficacy of iberdomide vs LEN in participants with NDMM after ASCT

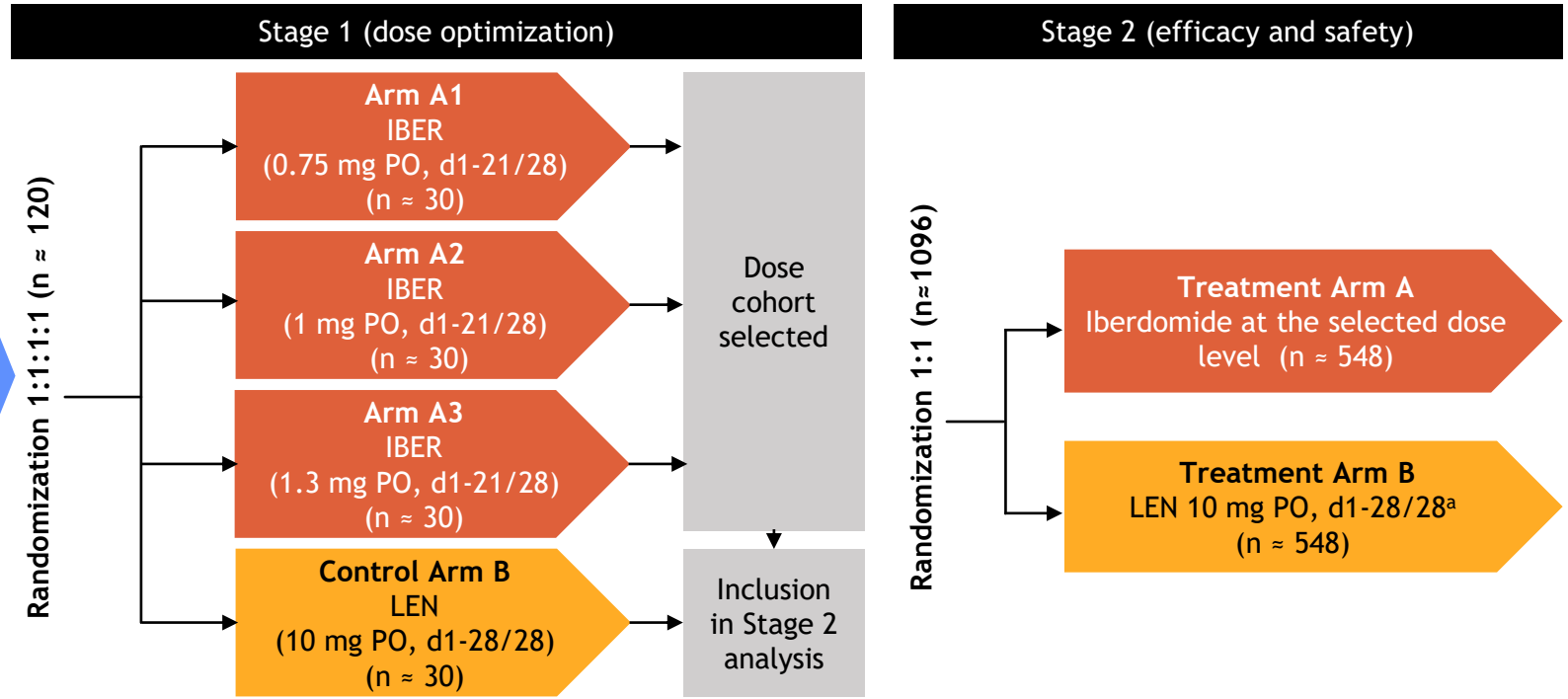
Adaptive study design dose corrects patients within the trial based on interim clinical outcomes

NDMM (N ≈ 1216)

Inclusion criteria
- Adult patients with confirmed diagnosis of symptomatic MM (IMWG criteria)
- Achieved ≥PR (according to IMWG 2016 criteria) to primary MM therapy (PI + IMiD +/- anti-CD38 or VCd and single or tandem ASCT +/- consolidation)

Exclusion criteria
- PD or clinical relapse (IMWG response criteria) following ASCT +/- consolidation or a disease that is not responsive to primary therapy

Stratification factors
- MRD: Negative vs positive/indeterminate
- Cytogenetic risk profile: High-risk vs standard-risk/indeterminate
- ISS at initial diagnosis: I and II vs III



Primary endpoint: PFS

Secondary endpoints: MRD negativity rate, **OS**, MRD conversion rate in participants with CR, sustainability of MRD negativity, RP3D, safety, PK Stage 1, PFS2, TTP, TTNT, best response achieved prior to PD (VGPR/sCR), HRQoL, recommended iberdomide dose for Stage 2

[a]If tolerated, dose can be increased to 15 mg from cycle 4 at the investigator's discretion.

ASCT, autologous stem cell transplantation; CD, cluster of differentiation; CR, complete response; d, day; HRQoL, health-related quality of life; IBER, iberdomide; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; ISS, international staging system; LEN, lenalidomide; MRD, minimal residual disease; MM, multiple myeloma; NDMM, newly diagnosed multiple myeloma; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PFS2, second progression-free survival; PI, proteasome inhibitor; PK, pharmacokinetics; PO, per oral; PR, partial response; RP3D, recommended phase 3 dose; sCR, stringent complete response; TTNT, time to next treatment; TTP, time to progression; VCd, bortezomib, cyclophosphamide, and dexamethasone; VGPR, very good partial response.

Reference: Gay F, et al. Presented at 2023 IMS Annual Meeting [abstract 137].

CC-220-MM-001: IBERDOMIDE + DARA-DEX, VD, OR KD
CELMOD TRIPLETS FOR RRMM

Iberdomide-Dara-dex (n = 43)

- 16.3% EMD
- Median 4 prior therapies
- 95.3% IMiD-refractory
- 86.0% PI-refractory
- 37.2% CD38 mAb-refractory
- 32.6% triple-class refractory
- Median duration of treatment: 4 cycles

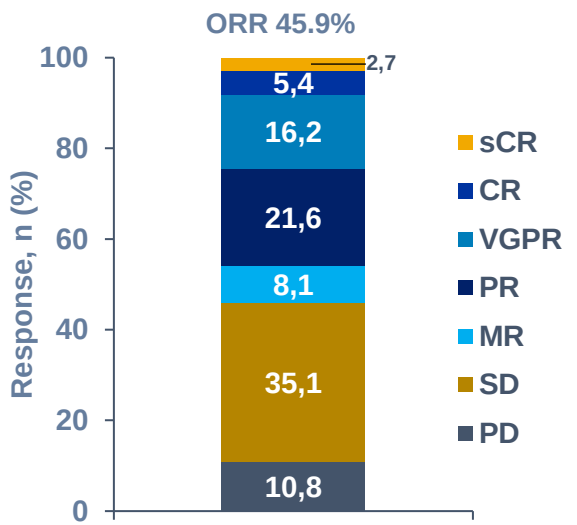
Iberdomide-Vd (n = 25)

- 16.0% EMD
- Median 5 prior therapies
- 80.0% IMiD-refractory
- 68.0% PI-refractory
- 80.0% CD38 mAb-refractory
- 48.0% triple-class refractory
- Median duration of treatment: 6 cycles

Iberdomide-Kd (n = 9)

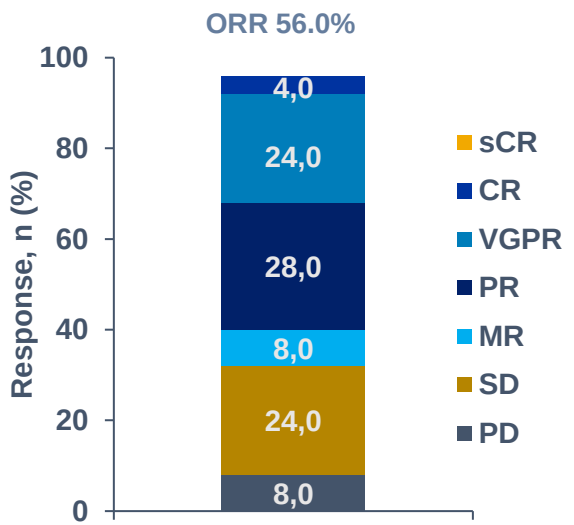
- 22.2% EMD
- Median 6 prior therapies
- 88.9% IMiD-refractory
- 66.7% PI-refractory
- 77.8% CD38 mAb-refractory
- 55.6% triple-class refractory
- Median duration of treatment: 5 cycles

Iberdomide-Dara-dex (n = 43)



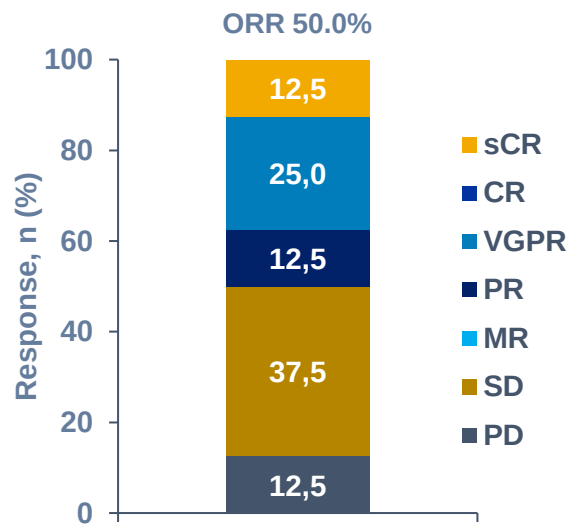
- Median DoR not reached
- Grade 3/4 hematologic AEs: neutropenia 12.8/53.8%, anemia 20.5/0%, thrombocytopenia 7.7/5.1%
- Grade 3 nonhematologic AEs: fatigue 2.6%, diarrhea 2.6%
- Infections 59.0% (grade 3/4: 10.3/5.1%)

Iberdomide-Vd (n = 25)



- Median DoR 35.7 weeks
- Grade 3/4 hematologic AEs: neutropenia 20/8%, anemia 12/0%, thrombocytopenia 4/20%
- Grade 3 nonhematologic AEs: diarrhea 4%, rash 4%
- Infections 68% (grade 3/4: 16/4%)

Iberdomide-Kd (n = 8)



- Median DoR not reached
- Grade 3/4 hematologic AEs (N=9): neutropenia 22.2/11.1%, anemia 0%, thrombocytopenia 0/11.1%
- Grade 3 nonhematologic AEs: fatigue 11.1%
- Infections 77.8% (grade 3/4: 22.2/11.1%)

AEs, adverse events; CR, complete response; DoR, duration of response; EMD, extramedullary disease; IMiD, immunomodulatory drug; Kd, carfilzomib-dexamethasone; MR, minimal response; NE, not evaluated; PD, progressive disease; PI, proteosome inhibitor; PR, partial response; RRMM, relapsed/refractory multiple myeloma; ORR, overall response rate; sCR, stringent complete response; SD, stable disease; Vd, bortezomib-dexamethasone; VGPR, very good partial response

1. Lonial. *HemaSphere*. 2021;5(S2):49-50, Abstract S187.

STUDY DESIGN: EXCALIBER RRMM (IBER-DD VS DVD IN 2L OR 3L RRMM)

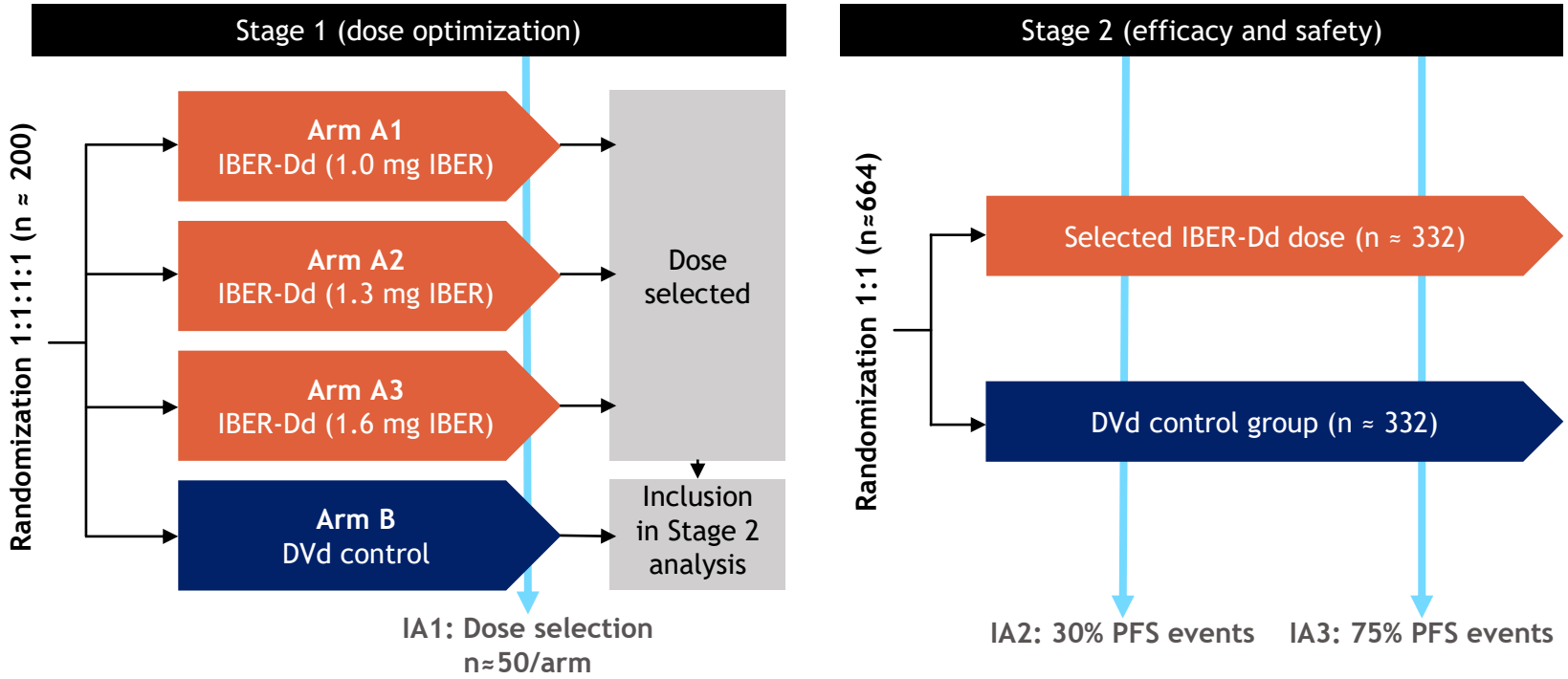
Objective: Evaluate the efficacy and safety of treatment with iberdomide, daratumumab, and dexamethasone (IBER-Dd) vs daratumumab, bortezomib, and dexamethasone (DVd) in patients with relapsed or refractory multiple myeloma (RRMM) with 1-2 prior lines of therapy

Phase 3, two-stage study adaptive design dose corrects patients within the trial based on interim clinical outcomes

RRMM with 1-2 prior LoT (N ≈ 864)

Inclusion Criteria
- Adult patients who received 1 to 2 prior lines of anti-myeloma therapy with progressive disease

Exclusion Criteria
- Patients who are refractory to bortezomib or an anti-CD38 therapy



Primary Endpoint: PFS
Secondary Endpoints: OS, MRD negativity rate, ORR, TTR, DoR, TTP, TTNT, PFS2, safety, and HRQoL

2L, second line; 3L, third line; CD, cluster of differentiation; D, daratumumab; d, dexamethasone; DoR, duration of response; HRQoL, health-related quality of life; IA, interim analysis; IBER, iberdomide; LoT, line of therapy; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PFS2, second progression-free survival; RRMM, relapsed/refractory multiple myeloma; TTNT, time to next treatment; TTP, time to progression; TTR, time to response; V, bortezomib.

Reference: Lonial S, et al. Presented at 2023 ASCO Annual Meeting [abstract 2132].

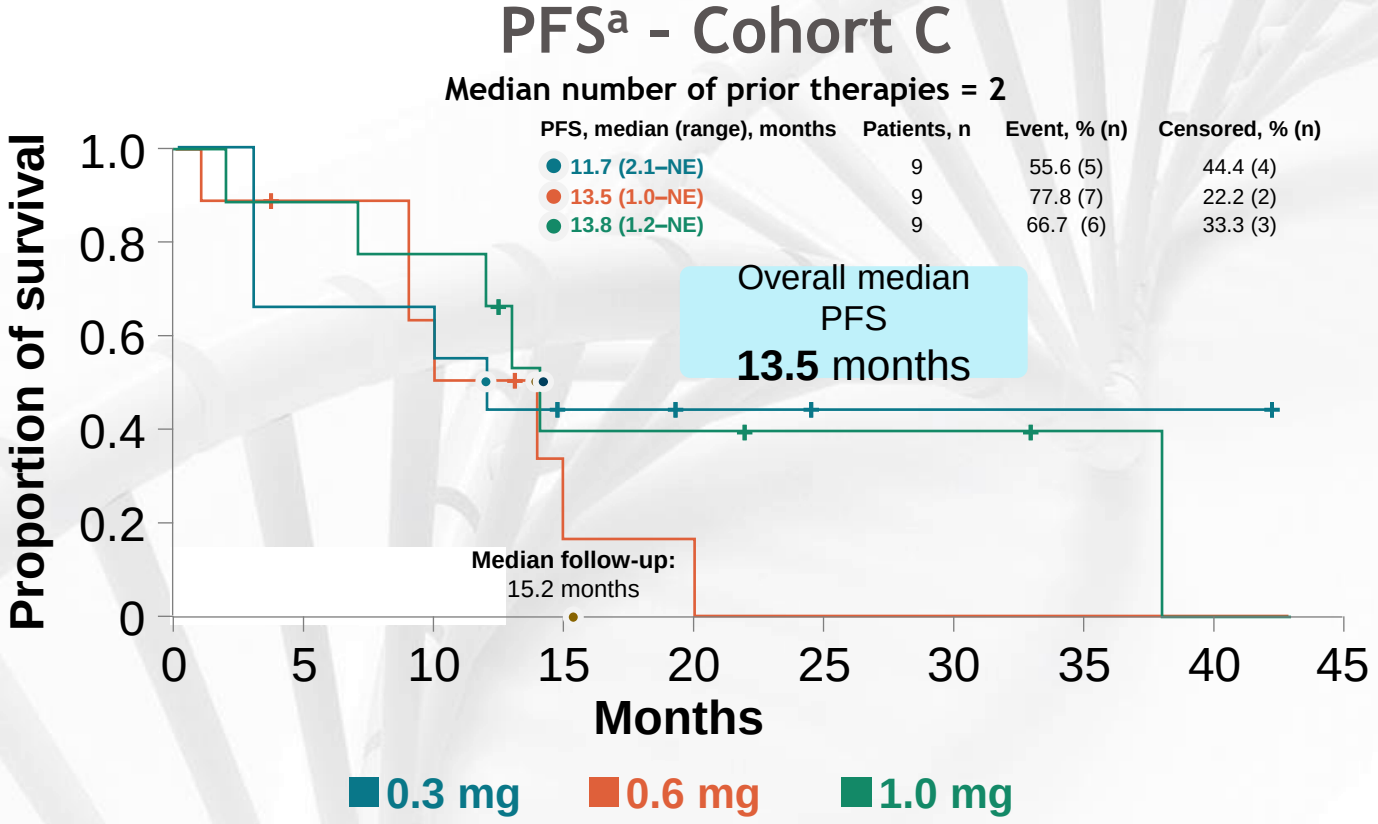
See IBER combo clinical data

See support for DVd as comparator

Bristol Myers Squibb Announces Phase 3 EXCALIBER-RRMM Study Evaluating Iberdomide in Combination with Standard Therapies Demonstrated a Significant Improvement in Minimal Residual Disease Negativity Rates in Relapsed or Refractory Multiple Myeloma

PRINCETON, N.J.--(BUSINESS WIRE)-- Bristol Myers Squibb (NYSE: BMY) today announced that the Phase 3 EXCALIBER-RRMM study evaluating iberdomide, an investigational cereblon E3 ligase modulator (CELMoD™), combined with standard therapies (daratumumab + dexamethasone) in patients with relapsed or refractory multiple myeloma (RRMM) demonstrated a statistically significant improvement in minimal residual disease (MRD) negativity rates, compared with the control arm, in a planned interim analysis of the MRD endpoint. The safety profile of iberdomide in combination with daratumumab and dexamethasone in this study is generally consistent with previous studies.

PFS IN DOSE-ESCALATION COHORT C (MEZIKD)



	All doses	1.0 mg
ORR,[b] % (95% CI)	85.2 (66.3-95.8)	77.8 (40.0-97.2)
DOR, median (95% CI), months	11.9 (6.4-35.9)	11.9 (0.2-NA)

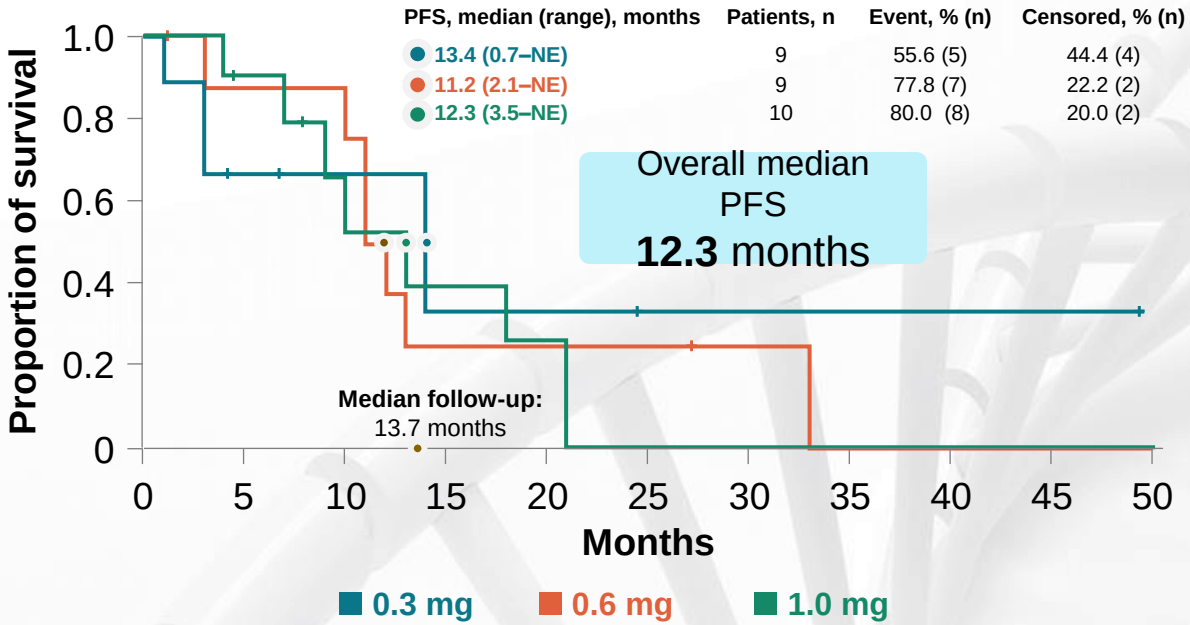
MeziKd showed efficacy at all dose levels tested with an overall median PFS of 13.5 months

Sandhu et al, ASH 2024

PHASE 1 CC-92480-MM-002: MEZI+VEL+DEX

PFS[a] – Cohort A

Median number of prior therapies = 3

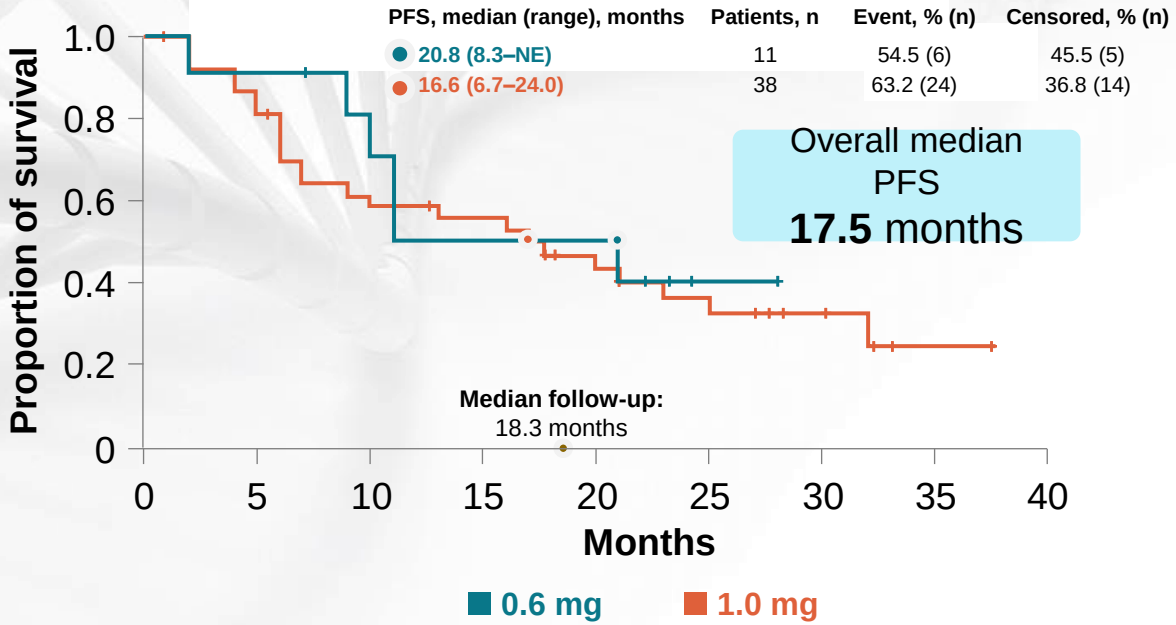


0.3 mg 0.6 mg 1.0 mg

	All doses	1.0 mg
ORR,[b] % (95% CI)	75.0 (55.1-89.3)	60.0 (55.1-89.3)
DOR, median (95% CI), months	10.9 (8.8-18.7)	11.6 (5.3-NA)

PFS[a] – Cohort D

Median number of prior therapies = 1



0.6 mg 1.0 mg

	All doses	1.0 mg
ORR,[b] % (95% CI)	85.7 (72.8-94.1)	84.2 (68.7-94.0)
DOR, median (95% CI), months	19.4 (9.7-NA)	19.4 (7.0-NA)

MeziVd showed durable efficacy at all dose levels tested with an overall median PFS > 1 year (17.5 months in Cohort D)

Sandhu et al, ASH 2024

STUDY DESIGN: SUCCESSOR-1 (MEZI-VD VS PVD IN 1-3 PRIOR LOT RRMM)

Objective: Compare the efficacy and safety of mezigdomide, bortezomib, and dexamethasone (MEZI-Vd) to that of pomalidomide, bortezomib, and dexamethasone (PVd) in patients with relapsed or refractory multiple myeloma (RRMM) and prior lenalidomide exposure

Phase 3, head-to-head study

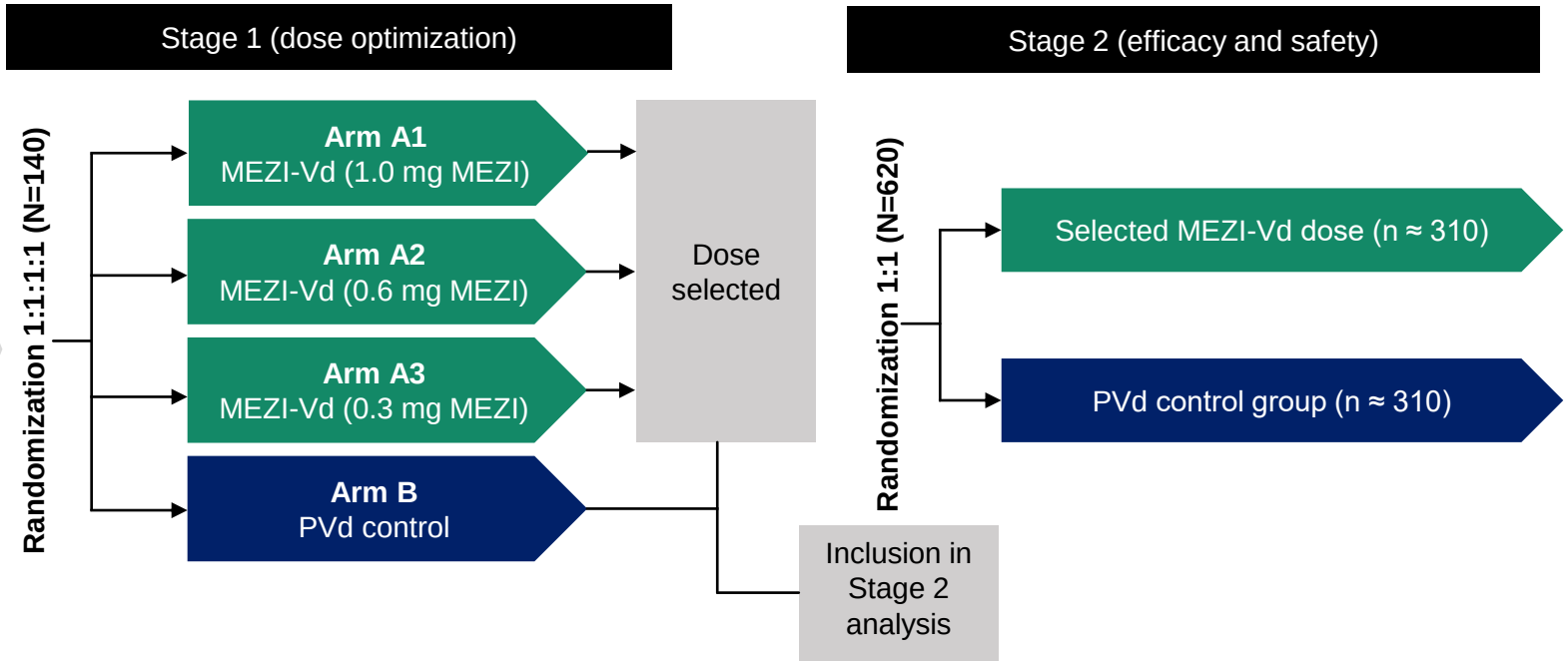
RRMM with 1-3 prior LoT

Key Inclusion Criteria

- Adult patients who received 1-3 prior lines of anti-myeloma therapy with progressive disease
  - Prior treatment with a lenalidomide-containing regimen
  - Minimal response or better to at least 1 prior therapy

Key Exclusion Criteria

- Patients with prior mezigdomide or pomalidomide exposure
- PI refractoriness (except to bortezomib dosed Q2W or less)
- Prior bortezomib treatment with best response <MR or discontinuation due to toxicity



Primary Endpoint: PFS

Secondary Endpoints: Determination of recommended mezigdomide dose in combination with Vd (Stage 1 only), PK analyses, OS, ORR, TTR, DoR, TTP, TTNT, PFS2, MRD negativity rate, Safety, HRQoL, and biomarker analyses

See MEZI combo clinical data

See support for PVd as comparator

d, dexamethasone; DoR, duration of response; HRQoL, health-related quality of life; LoT, line of therapy; MEZI, mezigdomide; MR, minimal response; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; P, pomalidomide; PFS, progression-free survival; PFS2, second progression-free survival; PI, proteasome inhibitor; PK, pharmacokinetics; Q2W, every 2 weeks; RRMM, relapsed/refractory multiple myeloma; TTNT, time to next treatment; TTP, time to progression; TTR, time to response; V, bortezomib.

Reference: Richardson PG, et al. 2023 SOHO Annual Meeting [abstract 372].

STUDY DESIGN: SUCCESSOR-2 (MEZI-KD VS KD IN 2L+ RRMM)

Objective: Compare the efficacy and safety of mezigdomide with carfilzomib and dexamethasone (MEZI-Kd) to that of carfilzomib and dexamethasone (Kd) in terms of PFS in participants with RRMM

Phase 3, two-stage seamless adaptive inferential design

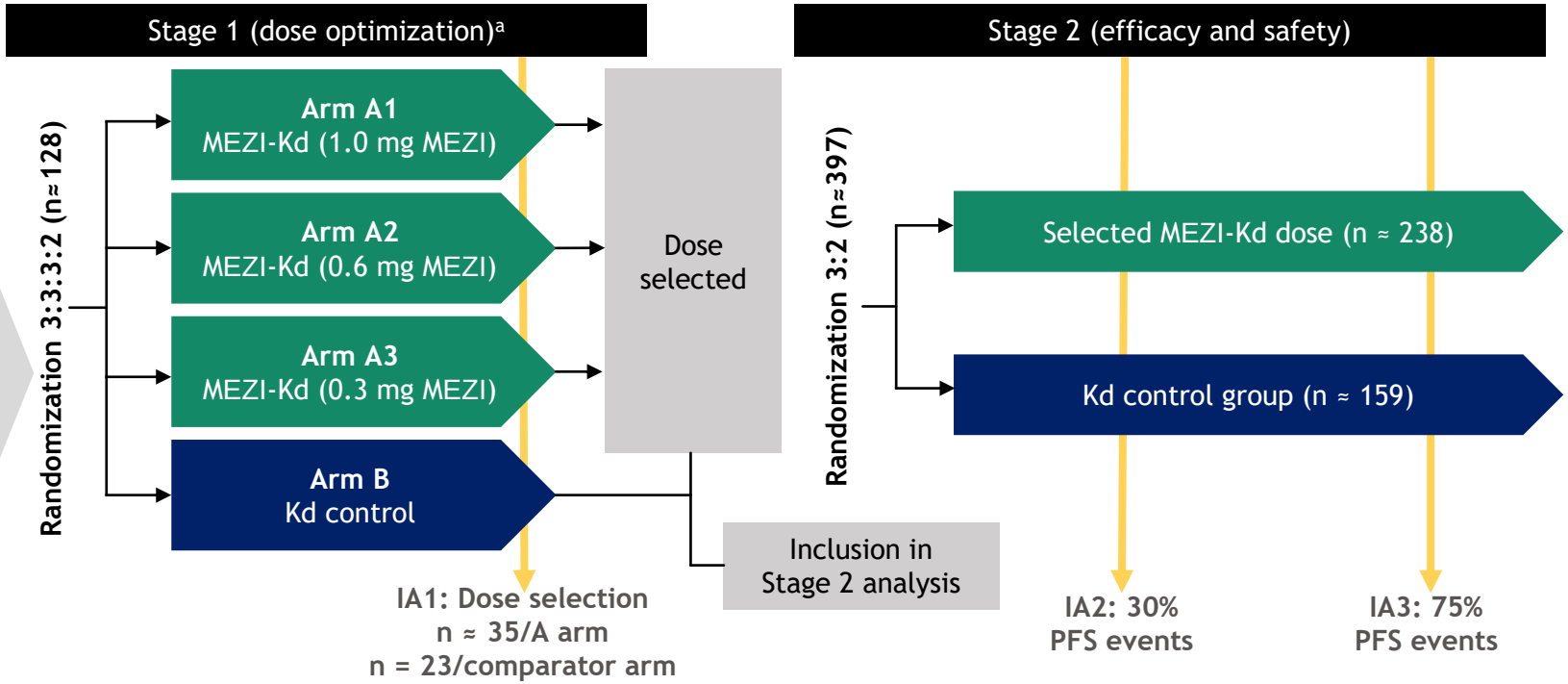
RRMM with ≥1 prior LoT (N ≈ 455)

Key Inclusion Criteria

- Adult patients who received ≥1 prior lines of anti-myeloma therapy with progressive disease
  - Prior treatment with **lenalidomide and an anti-CD38 monoclonal antibody**
  - Minimal response or better to at least 1 prior therapy

Key Exclusion Criteria

- Patients with prior mezigdomide or carfilzomib exposure
- Participant has previously received allogeneic stem cell transplant at any time or received autologous stem cell transplant within 12 weeks of initiating study treatment



Primary Endpoint: PFS

Secondary Endpoints: Recommended dose of mezigdomide (in Stage 1), OS, ORR, VGPRR, CR, MRD negativity rate, TTR, DoR, TTP, TTNT, PFS2, safety, and HRQoL

[a]Participant enrolled in Stage 1 on a dose of mezigdomide who is not chosen for Stage 2 will have the possibility to move to that dose if some criteria are met.

2L+, second line and beyond; CD, cluster of differentiation; CR, complete response; DoR, duration of response; HRQoL, health-related quality of life; IA, interim analysis; Kd, carfilzomib and dexamethasone; LoT, line of therapy; MEZI, mezigdomide; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PFS2, second progression-free survival; RRMM, relapsed/refractory multiple myeloma; TTNT, time to next treatment; TTP, time to progression; TTR, time to response; VGPRR, very good partial response rate.

Reference: Richardson PG, et al. Presented at 2023 ASCO Annual Meeting [abstract 8070].

See MEZI combo clinical data

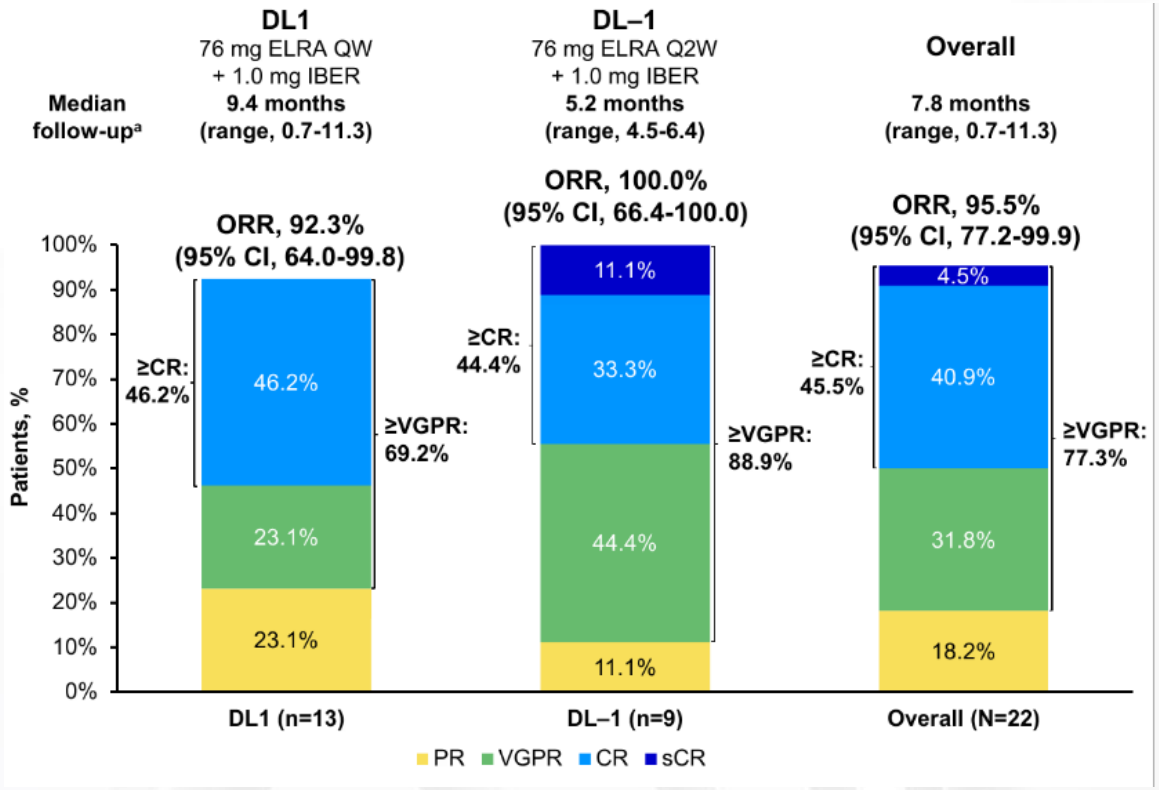
See support for Kd as comparator

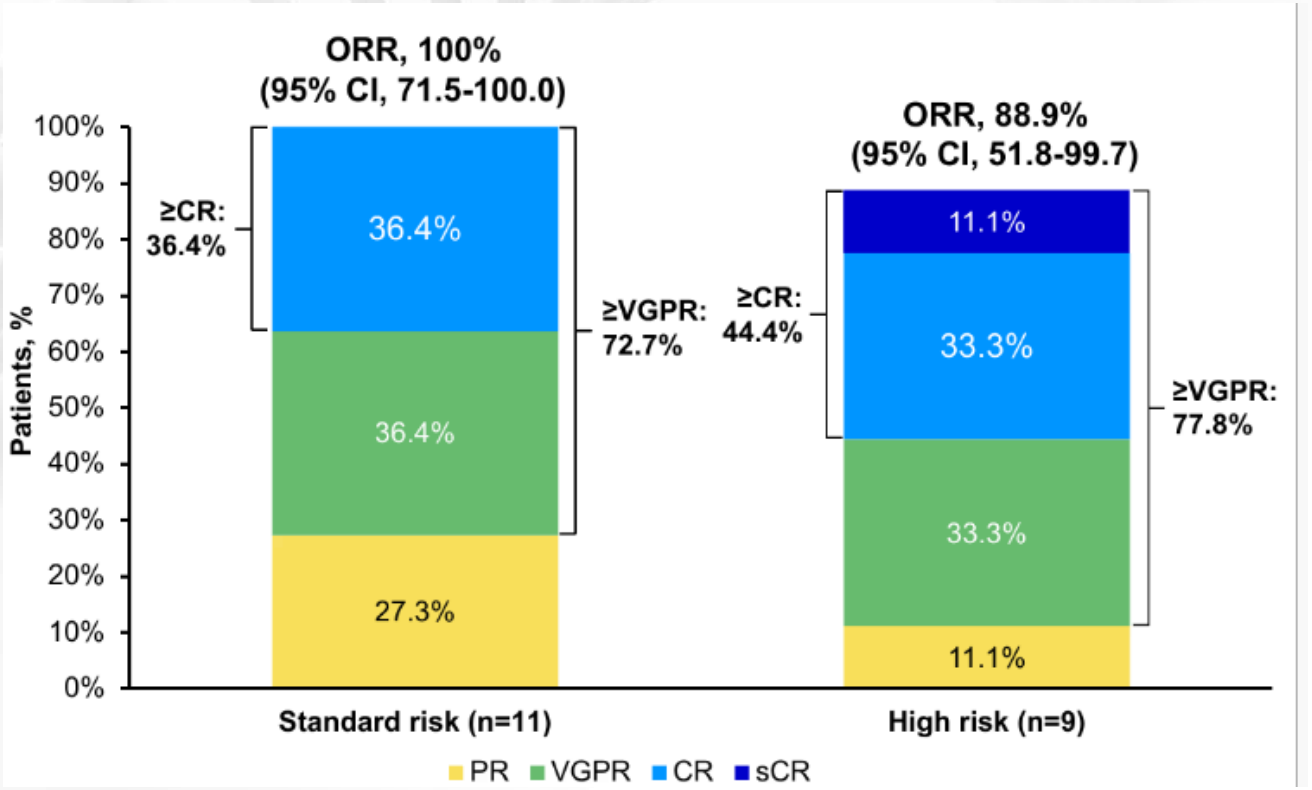
Bristol Myers Squibb Announces Positive Phase 3 Results from the SUCCESSOR-2 Study of Oral Mezigdomide in Relapsed or Refractory Multiple Myeloma

Study marks the first positive Phase 3 study for mezigdomide and the second positive Phase 3 study for the Bristol Myers Squibb CELMoD program

PRINCETON, N.J.--(BUSINESS WIRE)-- Bristol Myers Squibb (NYSE: BMY) today announced positive interim Phase 3 results from the SUCCESSOR-2 study (NCT05552976). In the trial, oral mezigdomide in combination with carfilzomib and dexamethasone (MeziKd) demonstrated statistically significant and clinically meaningful improvement in progression-free survival (PFS) versus carfilzomib and dexamethasone alone (Kd) in patients with relapsed or refractory multiple myeloma (RRMM). Safety findings were consistent with the known profile of mezigdomide and the combination regimen.

MAGNETISMM-30: ELRA + IBER





Suvannasankha *et al*; ASH 2025

MAGNETISMM-30: SAFETY

	N=22	
TEAE, n (%)[a]	Any grade	Grade 3/4
Any	22 (100.0)	19 (86.4)
Hematologic		
Neutropenia	17 (77.3)	16 (72.7)
Anemia	7 (31.8)	3 (13.6)
Lymphopenia	4 (18.2)	4 (18.2)
Nonhematologic		
CRS	15 (68.2)	0
Fatigue	14 (63.6)	0
Diarrhea	11 (50.0)	0
Headache	10 (45.5)	0
Cough	10 (45.5)	0
Nausea	9 (40.9)	1 (4.5)
Injection site reaction	9 (40.9)	0
Decreased appetite	8 (36.4)	1 (4.5)

Infections occurring in >5% of patients	N=22	
TEAE, n (%)[a]	Any grade	Grade 3
Infections[b]	9 (40.9)	2 (9.1)
Upper respiratory tract infection	6 (27.3)	0
Candida infection	3 (13.6)	0
Urinary tract infection	2 (9.1)	0

IVIG prophylaxis was administered approximately every 4 weeks to maintain IgG levels above 400 mg/dL

- All infections were grade ≤ 2 except for 1 event of each of grade 3 E coli gastroenteritis and grade 3 skin infection

PHASE I/II STUDY OF ELRANATAMAB + MEZIGDOMIDE

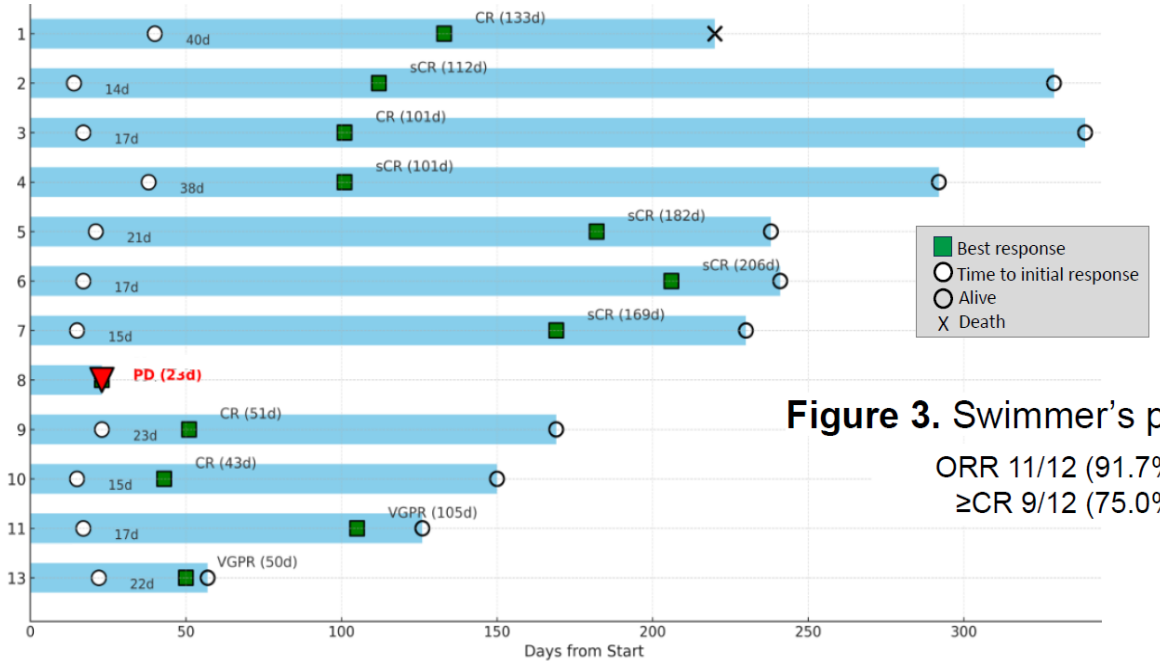


Figure 3. Swimmer's plot

ORR 11/12 (91.7%)
≥CR 9/12 (75.0%)

Safety (N = 12)	N (%)
CRS, all grades/gr ≥ 3	10 (83.3) / 0
ICANS, all grades/gr ≥ 3	0
Neutropenia, gr ≥ 3	7 (58.3)
During DLT period, gr ≥ 3	1 (8.3)
Thrombocytopenia, gr ≥ 3	6 (50.0)
During DLT period, gr ≥ 3	2 (16.7)
Infection, all grades	4 (33.3)*
Fatigue or weakness, all grades/gr ≥ 3	7 (58.3) / 0
Rash, all grades/gr ≥ 3	3 (25.0) / 0
Liver enzyme elevation, all gr/gr ≥ 3	3 (25.0) / 1 (8.3)

*6 episodes; 1 CMV retinitis, 1 csCMV, 2 pneumonia, 1 uveitis, 1 URI

AE, adverse events; CRS, cytokine release syndrome; DLT, dose-limiting toxicity; ICANS, immune effector cell-associated neurotoxicity syndrome.

Byun et al, ASH 2025, abstract #5845

SUMMARY AND FUTURE DIRECTIONS

- Iberdomide (CC-220) and Mezigdomide (CC-92480) are potent and well-tolerated therapies for the treatment of plasma cell dyscrasias and poised to become incorporated into standard of care across the treatment landscape
- Combination with standard myeloma therapies and now novel therapies have showed promising synergy with expected and tolerable safety profiles
- Potential role between TCR therapies or in combination with BsAb and CAR-T cell therapies to enhance efficacy